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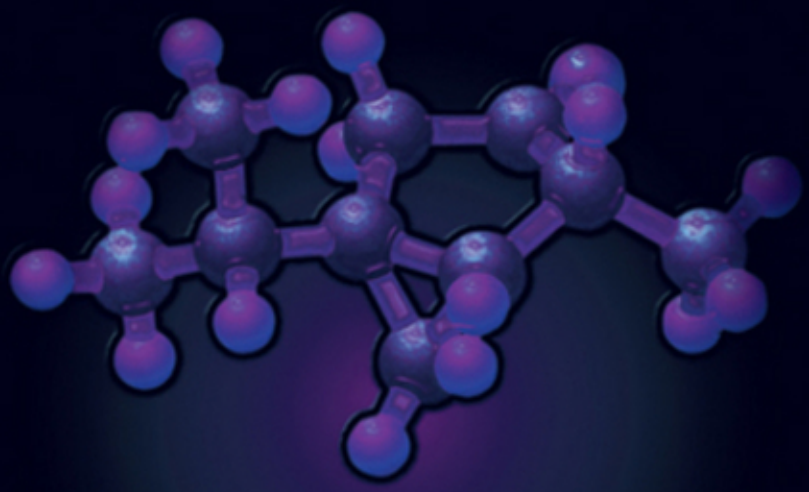

Handbook of Reagents for Organic Synthesis

Sulfur-Containing Reagents

Edited by

Leo A. Paquette

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for Organic Synthesis

Sulfur-Containing Reagents

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Sulfur-Containing Reagents

Edited by

Leo A. Paquette
The Ohio State University, Columbus, OH, USA

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This volume is dedicated to Dr. Gerald Berkelhammer who introduced me to the field of organosulfur chemistry during summer employment (1957) as a fledgling graduate student while working at the American Cyanamid Company in Stamford, Connecticut.

e-EROS Editorial Board

Contents

Preface

The eight-volume *Encyclopedia of Reagents for Organic Synthesis* (*EROS*), authored and edited by experts in the field, and published in 1995, had the goal of providing an authoritative multivolume reference work describing the properties and reactions of approximately 3000 reagents. With the coming of the Internet age and the continued introduction of new reagents to the field as well as new uses for old reagents, the electronic sequel, *e-EROS*, was introduced in 2002 and now contains in excess of 4000 reagents, catalysts, and building blocks making it an extremely valuable reference work. At the request of the community, the second edition of the encyclopedia, *EROS II*, was published in March 2009 and contains the entire collection of reagents at the time of publication in a 14 volume set.

Although the comprehensive nature of *EROS* and *EROS II* and the continually expanding *e-EROS* render them invaluable as reference works, their very size limits their practicability in a laboratory environment. For this reason, a series of inexpensive one-volume *Handbooks of Reagents for Organic Synthesis* (*HROS*), each focused on a specific subset of reagents, was introduced by the original editors of *EROS* in 1999:

Reagents, Auxiliaries, and Catalysts for C–C Bond Formation
Edited by Robert M. Coates and Scott E. Denmark

Oxidizing and Reducing Agents
Edited by Steven D. Burke and Rick L. Danheiser

Acidic and Basic Reagents
Edited by Hans J. Reich and James H. Rigby

Activating Agents and Protecting Groups
Edited by Anthony J. Pearson and William R. Roush

This series has continued over the past several years with the publication of another series of *HROS* volumes, each edited by a current or past member of the *e-EROS* editorial board:

Chiral Reagents for Asymmetric Synthesis
Edited by Leo A. Paquette

Reagents for High-Throughput Solid-Phase and Solution-Phase Organic Synthesis
Edited by Peter Wipf

Reagents for Glycoside, Nucleotide, and Peptide Synthesis
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Fluorine-Containing Reagents
Edited by Leo A. Paquette

Catalyst Components for Coupling Reactions
Edited by Gary A. Molander

Reagents for Radical and Radical Ion Chemistry
Edited by David Crich

This series now continues with this volume entitled *Sulfur-Containing Reagents*, edited by Leo Paquette, the originator and longtime guiding light of the *EROS* and *HROS* volumes, in addition to the online version, *e-EROS*. This 12th volume in the *HROS* series, like its predecessors, is intended to be an affordable, practicable compilation of reagents arranged around a central theme that it is hoped will be found at arm's reach from synthetic chemists worldwide. The reagents have been selected to give broad relevance to the volume, within the limits defined by the subject matter of organosulfur reagents. We have enjoyed putting this volume together and hope that our colleagues will find it as much enjoyable and useful to read and consult.

David Crich
Centre de Recherche de Gif-sur-Yvette
Institut de Chimie des Substances Naturelles
Gif-sur-Yvette, France

Introduction

The widespread use of sulfur-containing reagents by synthetic chemists is a reflection of the diversity of properties offered by this broad class of compounds. The enormous divergence in the reactivity of divalent and tetravalent sulfur reagents, the stereochemical issues offered by sulfoxides, and the ionizability of sulfonic acids represent only a few of the many facets of this collective group of reagents. The resulting demands placed on chemists for the appropriate adaptation of a given reagent emerge in many forms, not the least of which bear on one's knowledge of reactivity, availability of building blocks, appreciation of the consequences of associated changes in electronic character, and the like. As a consequence of many recent developments, it was deemed appropriate to incorporate into a single volume a compilation that brings together a large fraction of the more useful organosulfur reagents as well as key sulfur-containing promoters that are currently in vogue. As usual, the compilation has been arranged alphabetically in order to facilitate searching. An added benefit is to foster the scanning for information since proximal arrangements by compound type are not prevalent.

The selection covered in this volume is built on the many important discoveries at the hands of numerous practitioners of our science. These achievements have been realized in conjunction with a very extensive physical organic base.

The featured reagents have been culled from three sources. A minority of the entries appeared initially in the *Encyclopedia of Reagents for Organic Synthesis (EROS)*, which was published in 1995. Since that time, a significant number of entries involving these classical reagents have been updated (*e-EROS*), and this important add-on information is also found herein in the form of extensions to the original articles. The third pool of reagents is constituted of entirely new entries that detail the chemical and physical properties of an added subset of sulfur-containing compounds. In some instances, groups of reagents coincidentally appear in close proximity, thereby facilitating comparative analysis. Subsets consisting of *meta*- and *para*-nitrobenzenesulfonyl peroxide and of β-tosylethyl amine, hydrazine, and hydroxylamine are exemplary.

Among the opening segments of this volume is a section that illustrates those procedures relevant to the field that have appeared in volumes 65–85 of *Organic Syntheses*. It is hoped that these tried and tested protocols will provide a useful level of added guidance in selecting what course of action one might pursue. All in all, it is hoped that this handbook will prove to be a valued adjunct to researchers experienced in sulfur chemistry, and a particularly useful compilation for others seeking to gain a foothold in the field as expediently as possible. These goals will have been realized if advances materialize from exposure to its contents.

Leo A. Paquette
Department of Chemistry
The Ohio State University
Columbus, OH, USA

Short Note on InChIs and InChIKeys

The IUPAC International Chemical Identifier (InChI™) and its compressed form, the InChiKey, are strings of letters representing organic chemical structures that allow for structure searching with a wide range of online search engines and databases such as Google and PubChem. While they are obviously an important development for online reference works, such as *Encyclopedia of Reagents for Organic Reactions* (e-EROS), readers of this volume may be surprised to find printed InChi and InChIKey information for each of the reagents.

We introduced InChi and InChIKey to e-EROS in autumn 2009, including the strings in all HTML and PDF files. While we wanted to make sure that all users of e-EROS, the second print edition of EROS and all derivative Handbooks would find the same information, we appreciate that the strings will be of little use to the readers of the print editions, unless they treat them simply as reminders that e-EROS now offers the convenience of InChIs and InChIKeys, allowing the online users to make best use of their browsers and perform searches in a wide range of media.

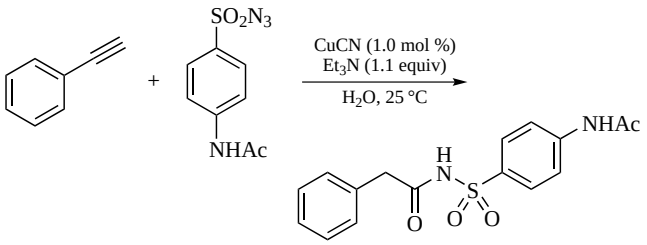
If you would like to know more about InChIs and InChIKeys, please go to the e-EROS website: www.mrw.interscience.wiley.com/eros/ and click on the InChI and InChiKey link.

Organic Synthesis Procedures Featuring the Synthesis of Organosulfur Compounds and Preparative Applications thereof, Volumes 65–85

Synthesis of Organosulfur Compounds

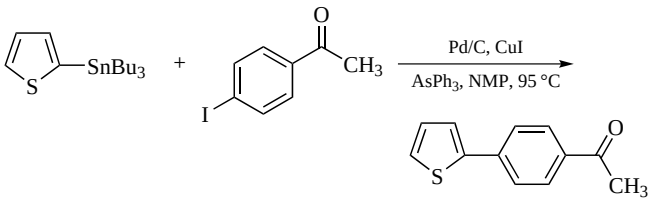
N-(4-Acetamidophenylsulfonyl)-2-phenylacetamide

S. H. Chol, S. J. Hwang, and S. Chang; *Org. Synth.* **2008**, *85*, 131.



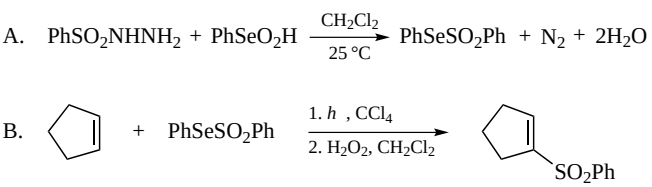
2-(4′-Acetylphenyl)thiophene

L. S. Liebeskind and E. Peña-Cabrera; *Org. Synth.* **2000**, *77*, 135.



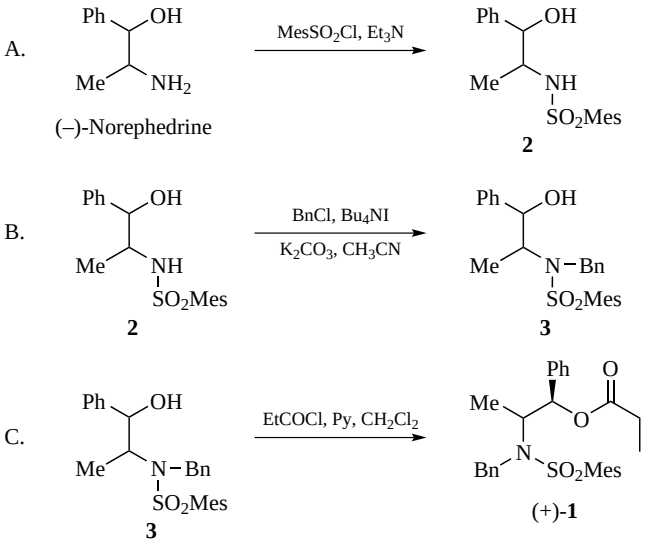
1-(Benzenesulfonyl)cyclopentane

H. S. Lin, M. J. Coghlan, and L. A. Paquette; *Org. Synth.* **1989**, *67*, 157.



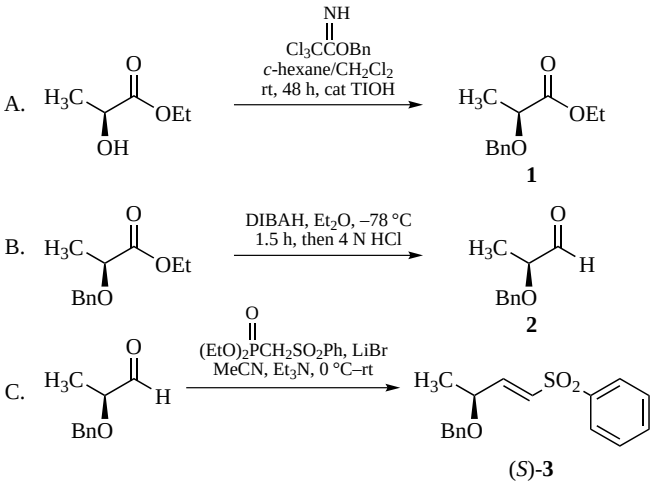
2-(*N*-Benzyl-*N*-mesitylenesulfonyl)amino-1-phenyl-1-propyl Propionate

A. Abiko; *Org. Synth.* **2003**, *19*, 109.



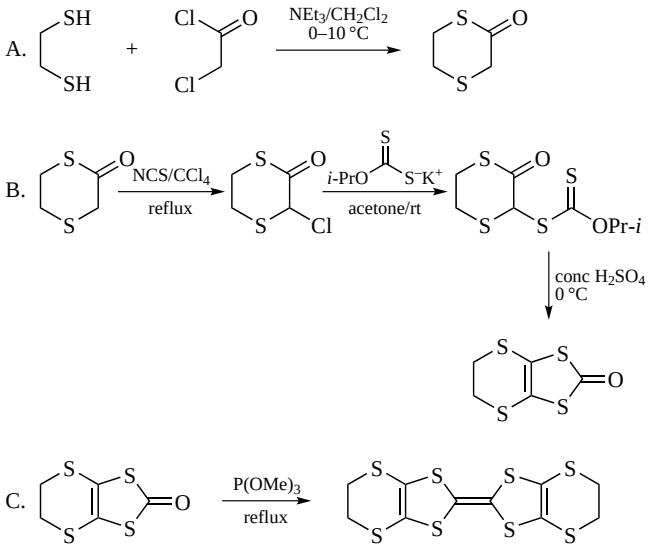
(−)-(*E*,*S*)-3-(Benzyloxy)-1-butenyl Phenyl Sulfone

D. Enders, S. Von Berg, and B. Jandeleit; *Org. Synth.* **2002**, *78*, 177.



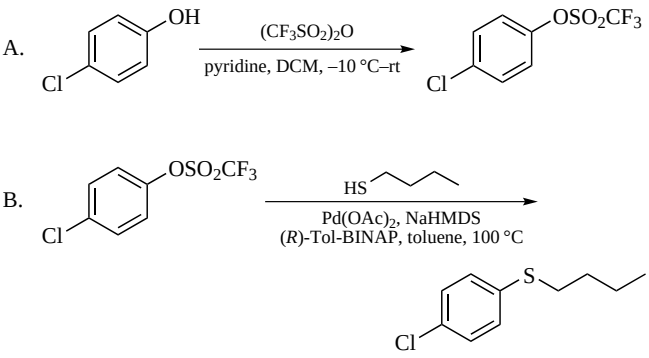
2,2′-Bi-5,6-dihydro-1,3-dithiolo[4,5-*b*][1,4]dithiinylidene (BEDT-TTF)

J. Larsen and C. Lenoir; *Org. Synth.* **1995**, *72*, 265.



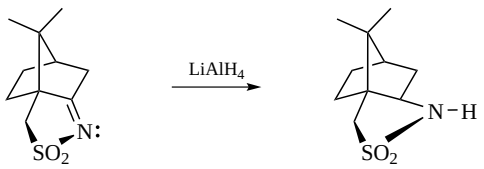
n-Butyl 4-Chlorophenyl Sulfide

J. C. McWilliams, F. Fleitz, N. Zheng, and J. D. Armstrong III; *Org. Synth.* **2003**, *79*, 43.



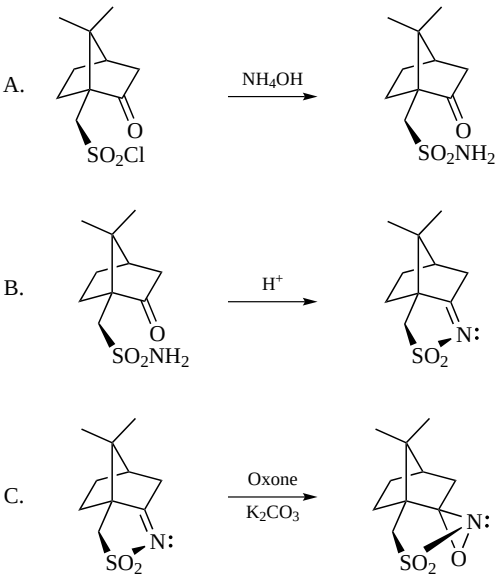
(−)-D-2, 10-Camphorsultam

M. C. Weismiller, J. C. Towson, and F. A. Davis; *Org. Synth.* **1990**, *69*, 154.



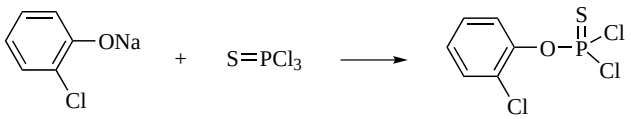
(+)-(2*R*,8a*S*)-10-(Camphorylsulfonyl)oxaziridine

J. C. Towson, M. C. Weismiller, G. S. Lal, A. C. Sheppard, and F. A. Davis; *Org. Synth.* **1990**, *69*, 158.



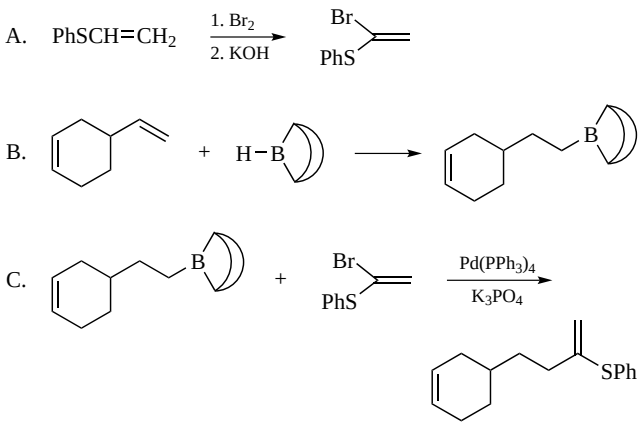
2-Chlorophenyl Phosphorodichloridothioate

V. T. Ravikumar and B. Ross; *Org. Synth.* **1999**, *76*, 271.



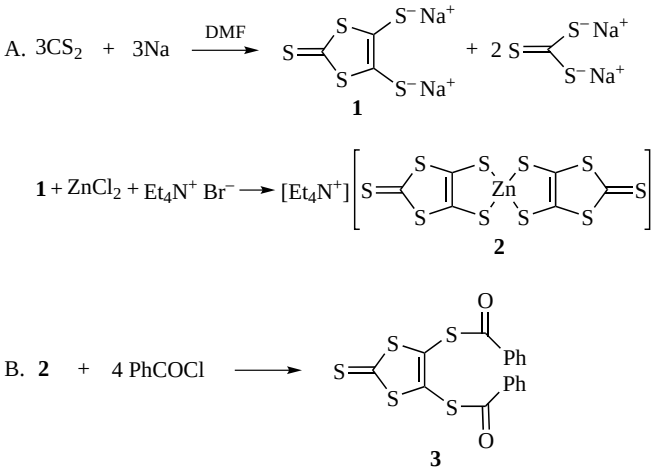
4-(3-Cyclohexenyl)-2-phenylthio-1-butene

T. Ishiyama, N. Miyaura, and A. Suzuki; *Org. Synth.* **1993**, *71*, 89.



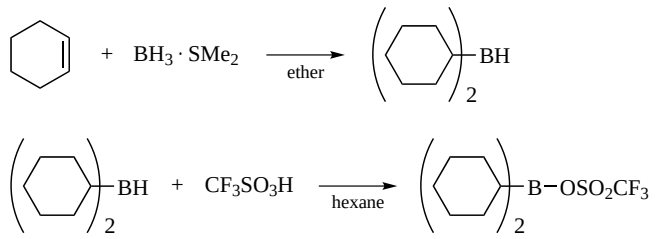
4,5-Dibenzoyl-1,3-dithiole-1-thione

T. K. Hansen, J. Becher, T. Jørgensen, K. S. Varma, R. Khedekar, and M. P. Cava; *Org. Synth.* **1976**, *73*, 270.



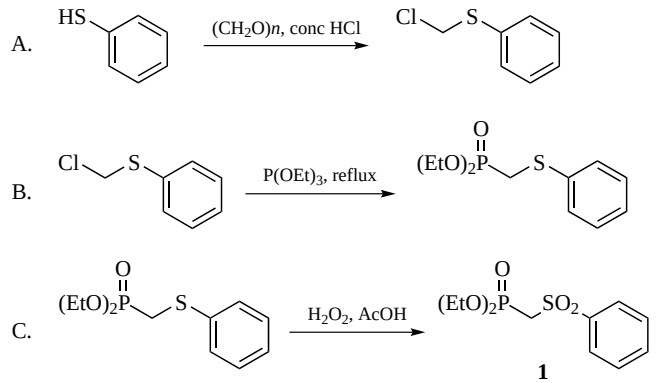
Dicyclohexylboron Trifluoromethanesulfonate

A. Abiko; *Org. Synth.* **2003**, *78*, 103.



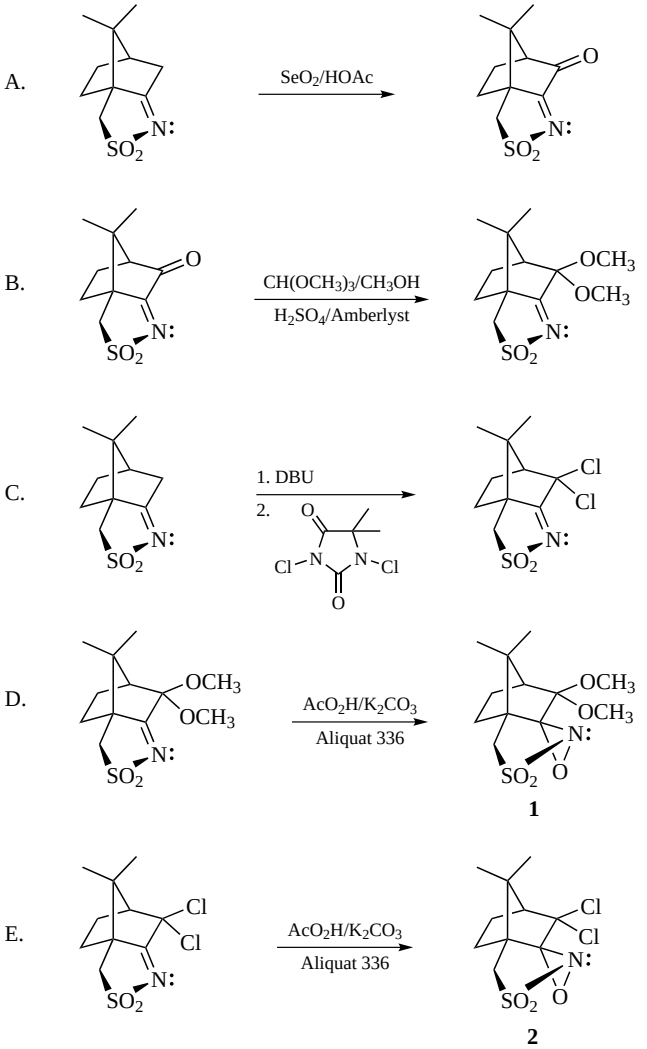
Diethyl [(Phenylsulfonyl)methyl]phosphonate

D. Enders, S. von Berg, and B. Jandeleit; *Org. Synth.* **2002**, *78*, 169.



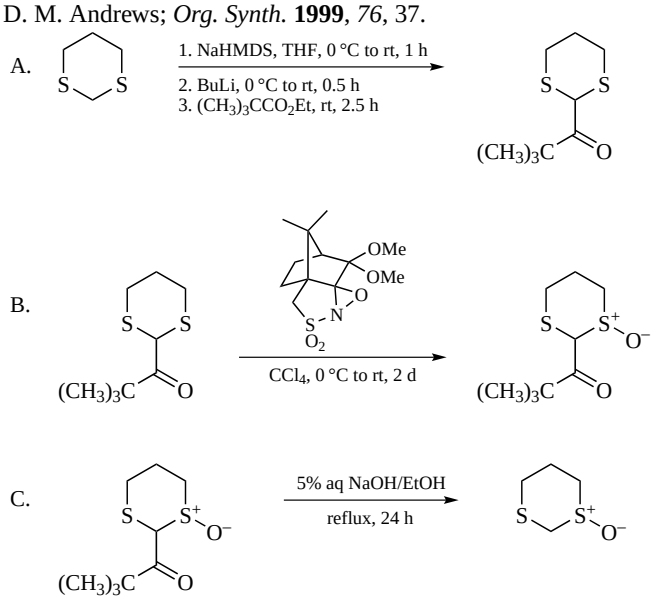
(+)-(2*R*,8a*R)-[(8,8-Dimethoxycamphoryl)sulfonyl]oxaziridine and (+)-(2*R*,8a*R**)-[(8,8-Dichlorocamphoryl)sulfonyl]oxaziridine**

B.-C. Chen, C. K. Murphy, A. Kumar, R. T. Reddy, C. Clark, P. Zhou, B. M. Lewis, D. Gala, I. Mergelsberg, D. Scherer, J. Buckley, D. DiBenedetto, and F. A. Davis; *Org. Synth.* **1995**, *93*, 159.



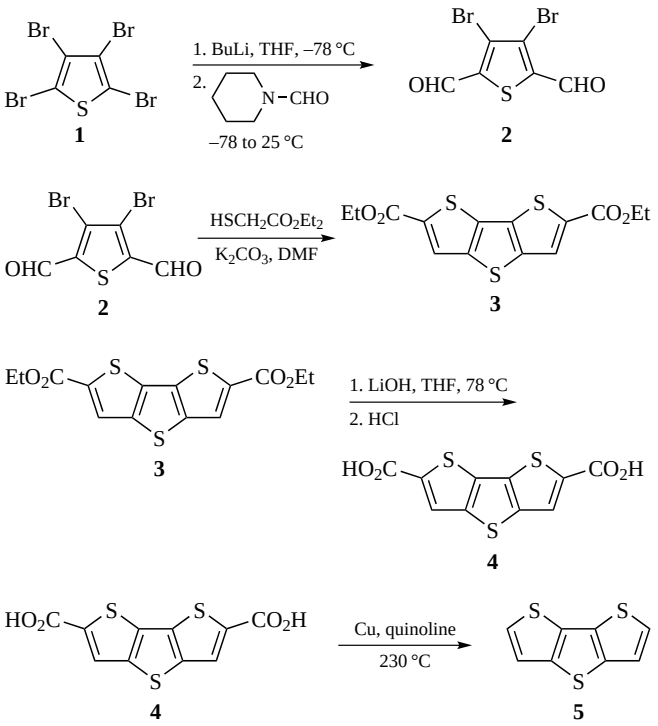
1*S*-(−)-1,3-Dithiane 1-Oxide

P. C. Bulman Page, J. P. Heer, D. Bethell, E. W. Collington, and D. M. Andrews; *Org. Synth.* **1999**, *76*, 37.



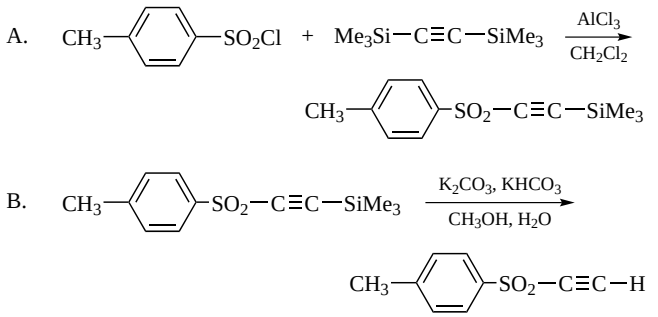
Dithieno[3,2-*b*:2′,3′-*d*]thiophene

J. Frev, S. Proemmel, M. A. Armitage, and A. B. Holmes; *Org. Synth.* **2006**, *83*, 209.



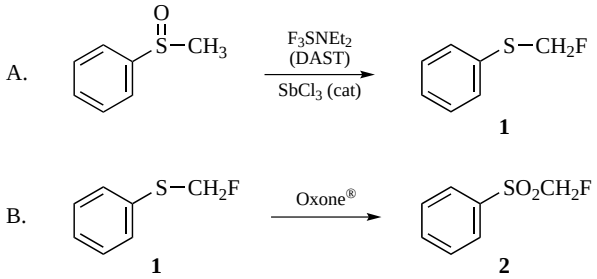
Ethynyl *p*-Tolyl Sulfone

L. Waykole and L. A. Paquette; *Org. Synth.* **1989**, *67*, 149.



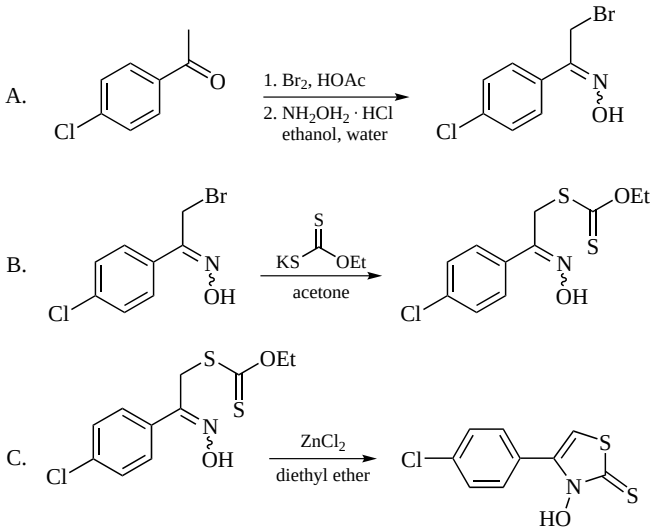
Fluoromethyl Phenyl Sulfone

J. R. McCarthy, D. P. Matthews, and J. P. Paolini; *Org. Synth.* **1995**, *72*, 209.



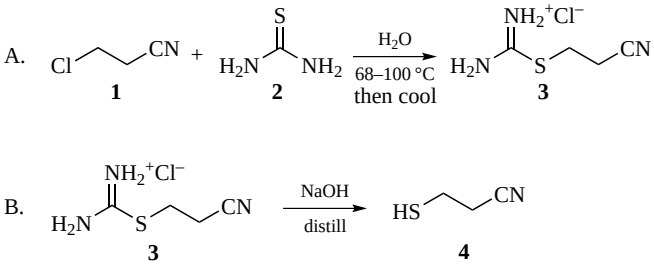
N-Hydroxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione

J. Hartung and M. Schwarz; *Org. Synth.* **2003**, *79*, 228.



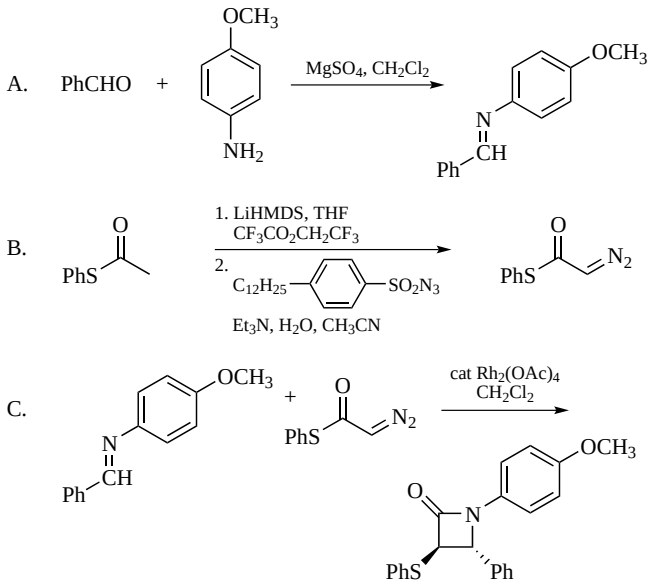
β-Mercaptopropionitrile (2-Cyanoethanethiol)

R. E. Gerber, C. Hasbun, L. G. Dubenko, M. F. King, and D. E. Bierer; *Org. Synth.* **2000**, *77*, 186.



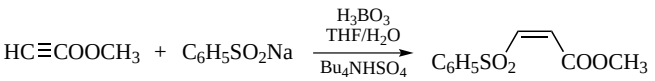
trans-1-(4-Methoxyphenyl)-4-phenyl-3-(phenylthio)azetidin-2-one

R. L. Danheiser, I. Okamoto, M. D. Lawlor, and T. W. Lee; *Org. Synth.* **2003**, *80*, 160.



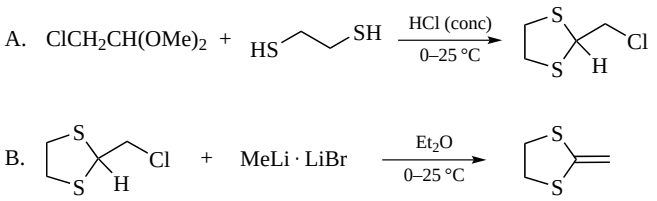
Methyl (*Z*)-3-(Benzenesulfonyl)prop-2-enoate

G. C. Hirst and P. J. Parsons; *Org. Synth.* **1990**, *69*, 169.



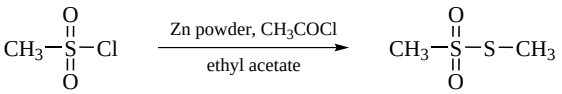
2-Methylene-1,3-dithiolane

K. R. Dahnke and L. A. Paquette; *Org. Synth.* **1993**, *71*, 175.



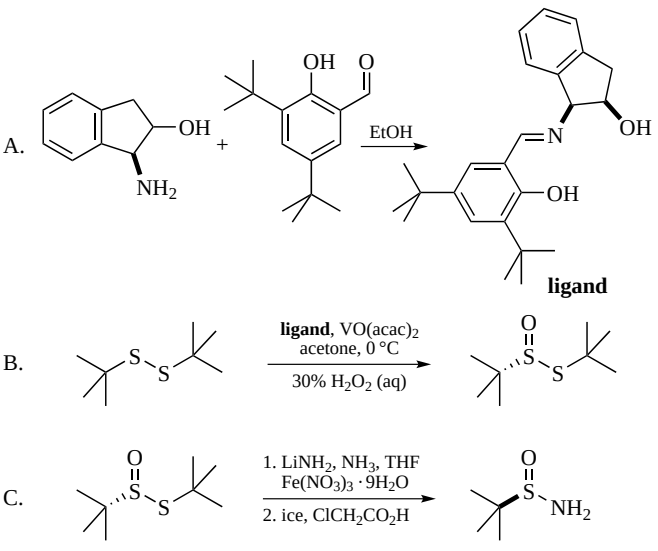
***S*-Methyl Methanethiosulfonate**

F. Chemla and P. Karoyan; *Org. Synth.* **2002**, *78*, 99.



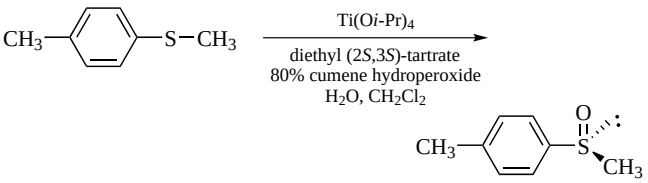
(R_s)-(+)-2-Methyl-2-propanesulfinamide

D. J. Weix and J. A. Ellman; *Org. Synth.* **2005**, *82*, 157.



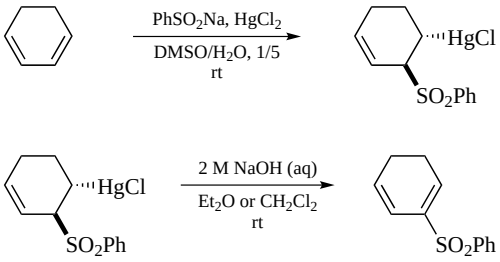
(*S*)-(−)-Methyl *p*-Tolyl Sulfoxide

S. H. Zhao. O. Samuel, and H. B. Kagan; *Org. Synth.* **1990**, *68*, 49.



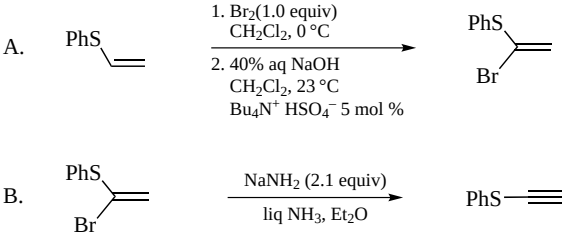
2-(Phenylsulfonyl)-1,3-cyclohexadiene

J.-E. Bäckvall, S. K. Juntunen, and O. S. Andell; *Org. Synth.* **1990**, *68*, 148.



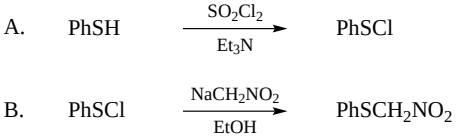
Phenylthioacetylene

P. A. Magriotis and J. T. Brown; *Org. Synth.* **1995**, *72*, 252.



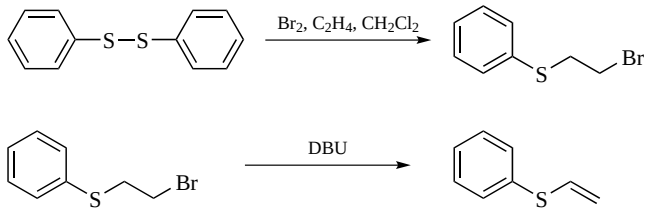
(Phenylthio)nitromethane

A. G. M. Barrett, D. Dhanak, G. G. Graboski, and S. J. Taylor; *Org. Synth.* **1990**, *68*, 8.



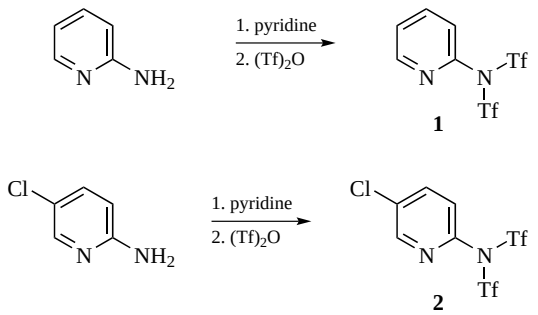
Phenyl Vinyl Sulfide

D. S. Reno and R. J. Pariz; *Org. Synth.* **1997**, *74*, 124.



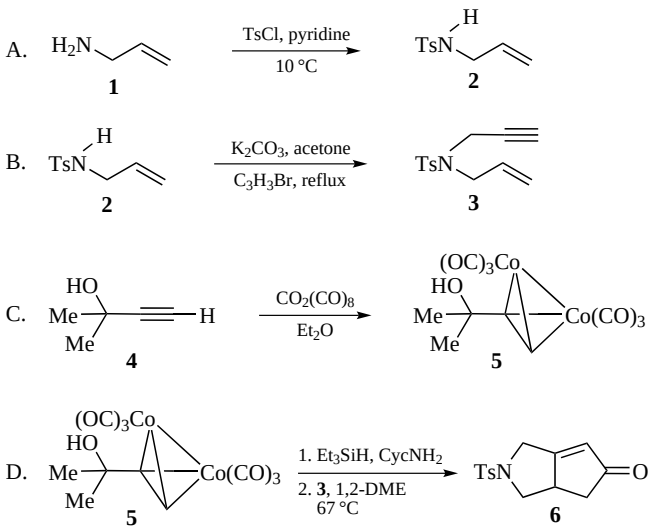
***N*-(2-Pyridyl)triflimide and *N*-(5-Chloro-2-pyridyl)triflimide**

D. L. Comins, A. Dehghani, C. J. Foti, and S. P. Joseph; *Org. Synth.* **1997**, *74*, 77.



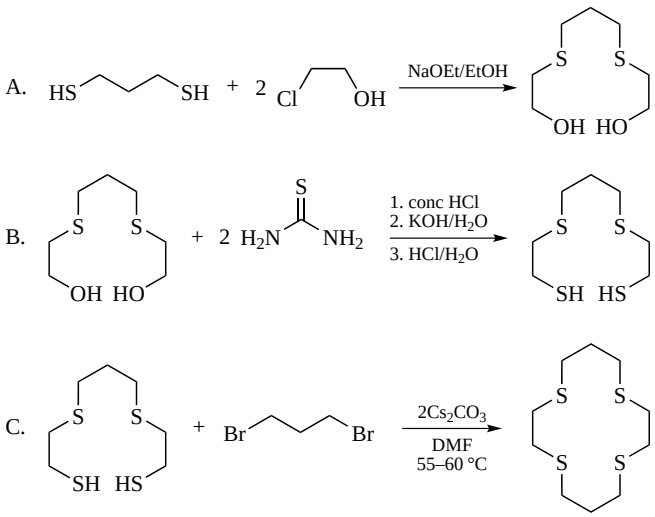
2,3,3α,4-Tetrahydro-2-[(4-methylbenzene) sulfonyl]cyclopenta[*c*]pyrrol-5(1*H*)-one

M. C. Patel, T. Livinghouse, and B. L. Pagenkopf; *Org. Synth.* **2003**, *80*, 93.



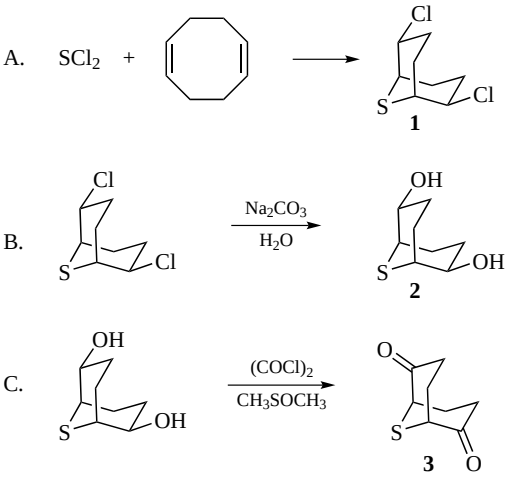
1,4,8,11-Tetrathiacyclotetradecane

J. Buter and R. M. Kellogg; *Org. Synth.* **1987**, *65*, 150.



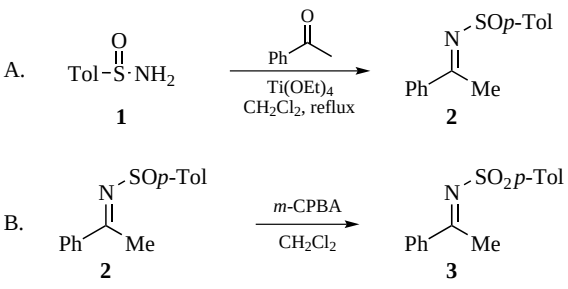
9-Thiabicyclo[3.3.1]nonane-2,6-dione

R. Bishop; *Org. Synth.* **1992**, *70*, 120.



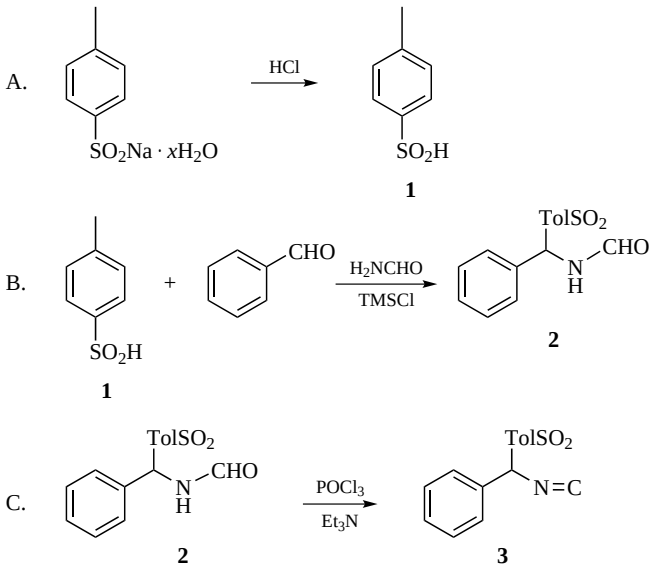
***N*-*p*-Tolylsulfonyl-(*E*)-1-Phenylethylideneimine**

J. L. G. Ruano, J. Aleman, A. Parra, and M. B. Cid; *Org. Synth.* **2007**, *84*, 129.



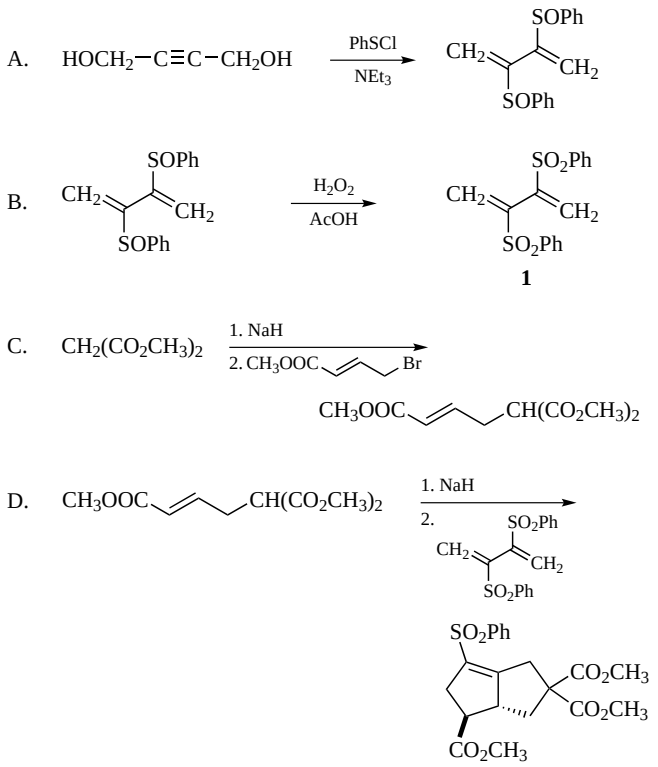
α-Tosylbenzyl Isocyanide

J. Sisko, M. Mellinger, P. W. Sheldrake, and Neil H. Baine; *Org. Synth.* **2000**, *77*, 198.



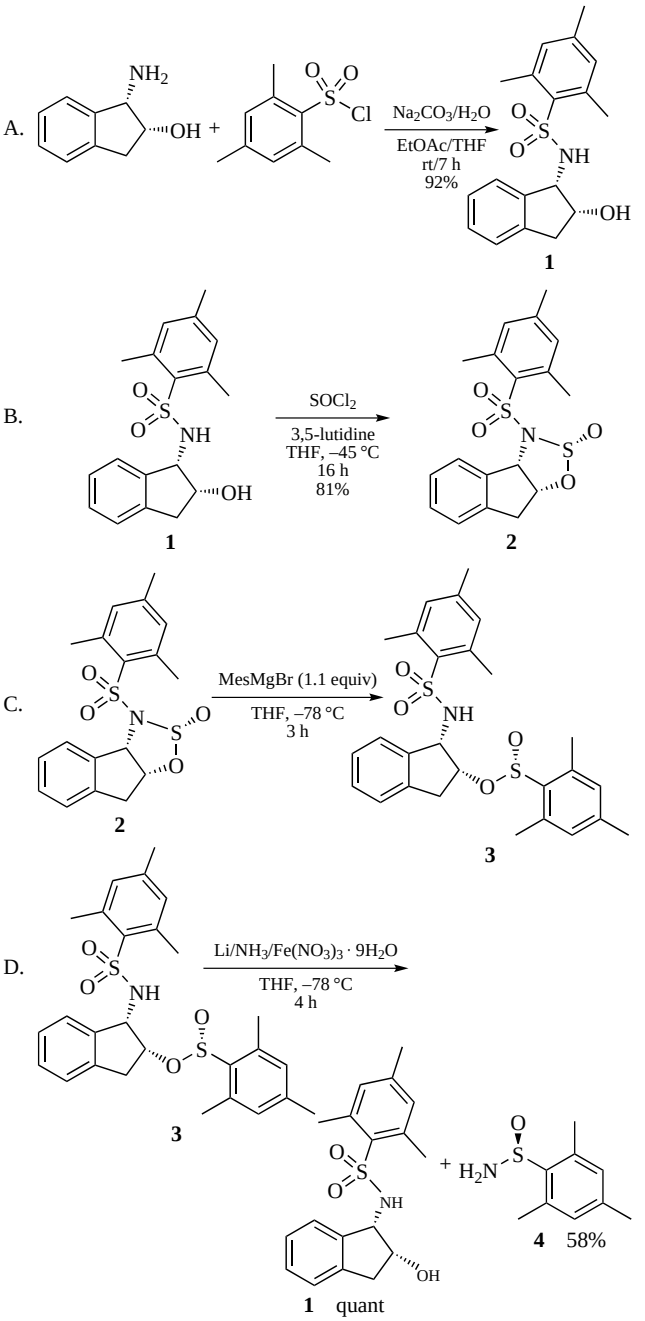
trans-4,7,7-Tricarbomethoxy-2-phenylsulfonylbicyclo[3.3.0]oct-1-ene

A. Padwa, S. H. Watterson, and Z. Ni; *Org. Synth.* **1997**, *74*, 147.



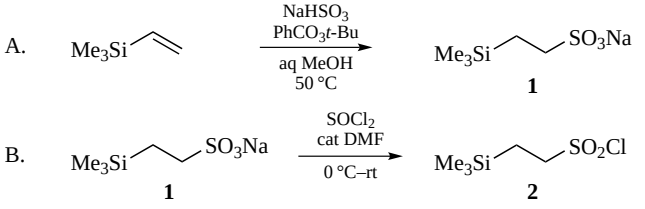
(*S*)-(+)-2,4,6-Trimethylbenzenesulfinamide

T. Ramachandar, Y. Wu, J. Zhang, and F. A. Davis; *Org. Synth.* **2006**, *83*, 131.



2-Trimethylsilylethanesulfonyl Chloride

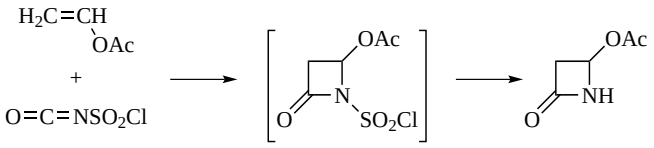
S. M. Weinreb, C. E. Chase, P. Wipf, and S. Venkatraman; *Org. Synth.* **1998**, *75*, 161.



Synthetic Applications of Sulfur-Containing Compounds

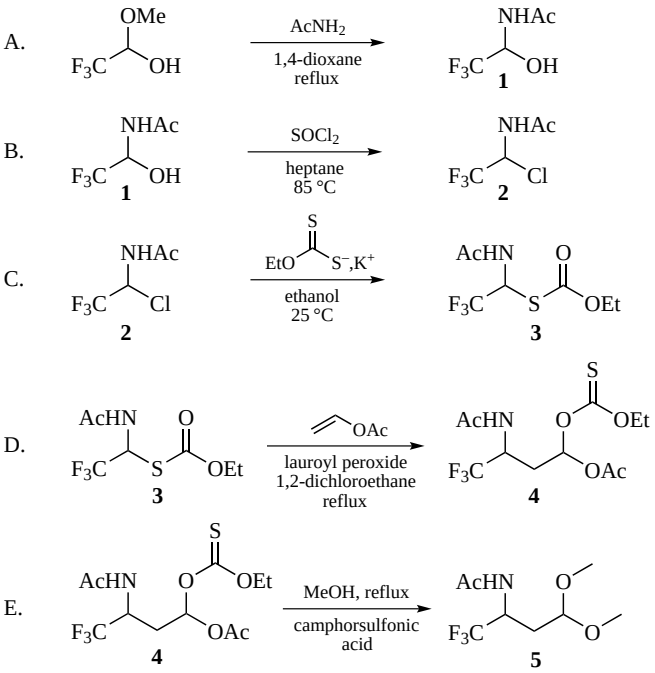
4-Acetoxyazetidin-2-one

S. J. Mickel, C.-N. Hsiao, and M. J. Miller; *Org. Synth.* **1987**, *65*, 135.



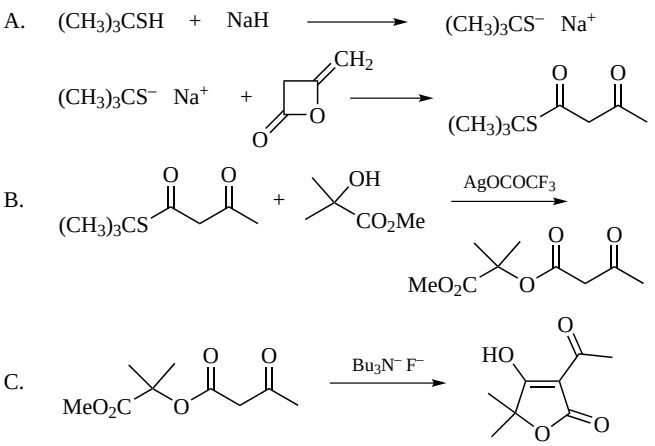
2-(*N*-Acetylamino)-4,4-dimethoxy-1,1,1-trifluorobutane

F. Gagosz and S. Z. Zard; *Org. Synth.* **2007**, *84*, 32.



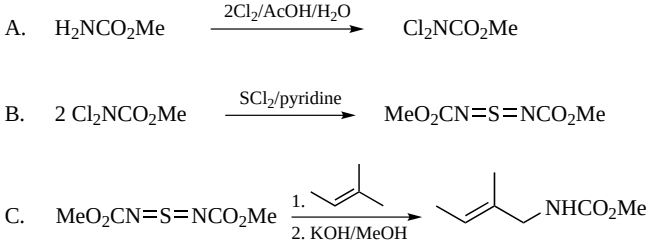
3-Acetyl-4-hydroxy-5,5-dimethylfuran-2(5*H*)-one

C. M. J. Fox and S. V. Ley; *Org. Synth.* **1988**, *66*, 108.



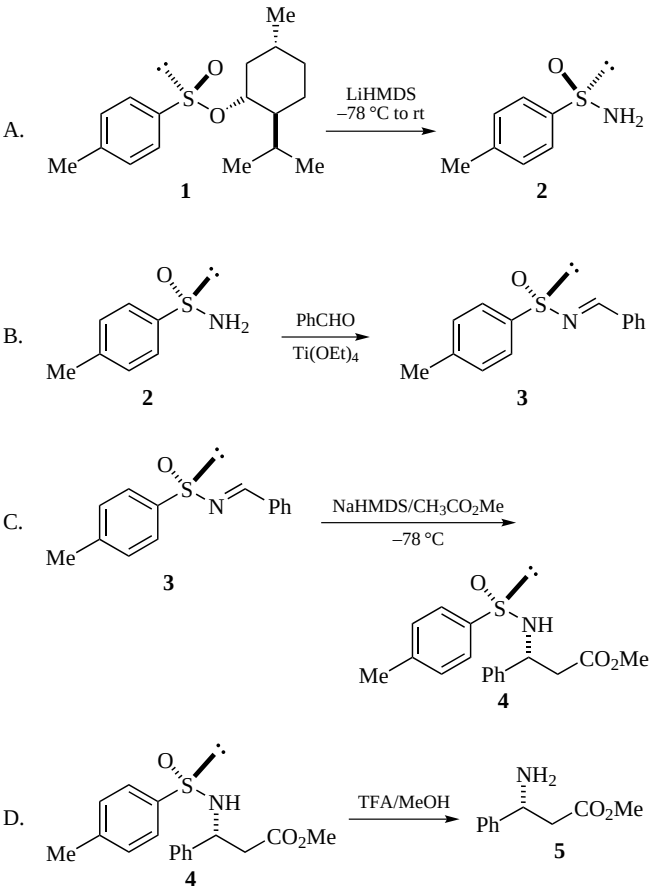
Allylcarbamates by the Aza-ene Reaction: Methyl *N*-(2-methyl-2-butenyl)carbamate

G. Kresze, H. Braxmeier, and H. Münsterer; *Org. Synth.* **1987**, *65*, 159.



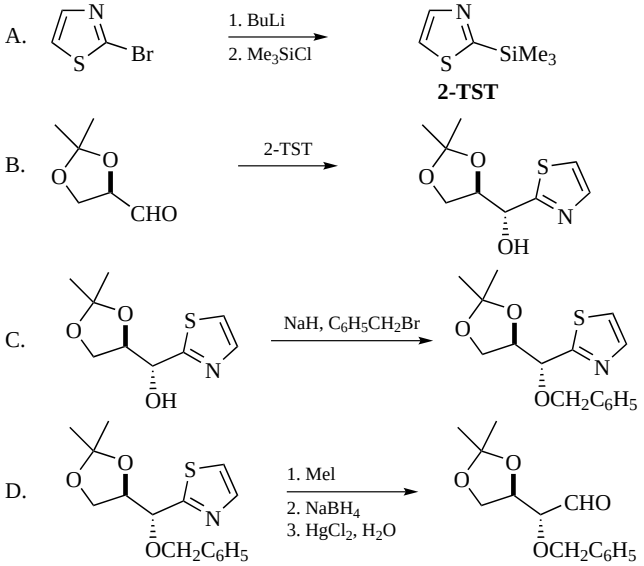
Asymmetric Synthesis of Methyl (*R*)-(+)-*β*-Phenylalanate from (*S*)-(+)*N*-(Benzylidene)-*p*-toluenesulfinamide

D. L. Fanelli, J. M. Szewczyk, Y. Zhang, G. V. Reddy, D. M. Burns, and F. A. Davis; *Org. Synth.* **2000**, *77*, 50.



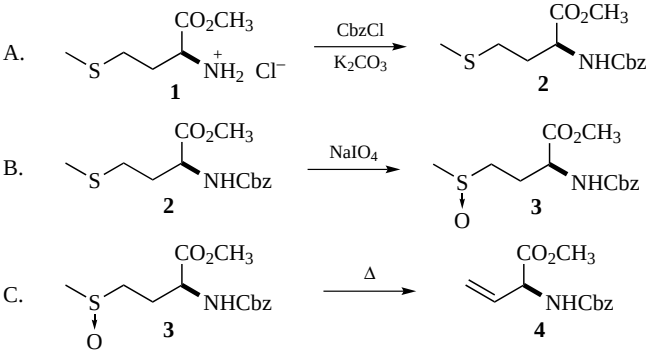
2-*O*-Benzyl-3,4-isopropylidene-D-erythrose

A. Dondoni and P. Merino; *Org. Synth.* **1995**, *72*, 21.



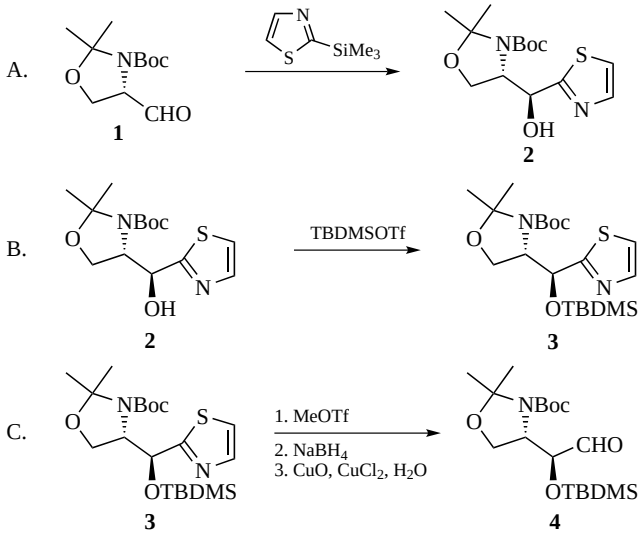
N-(Benzyloxycarbonyl)-L-vinylglycine Methyl Ester

M. Carrasco, R. J. Jones, S. Kamel, H. Rapoport; *Org. Synth.* **1992**, *70*, 29.



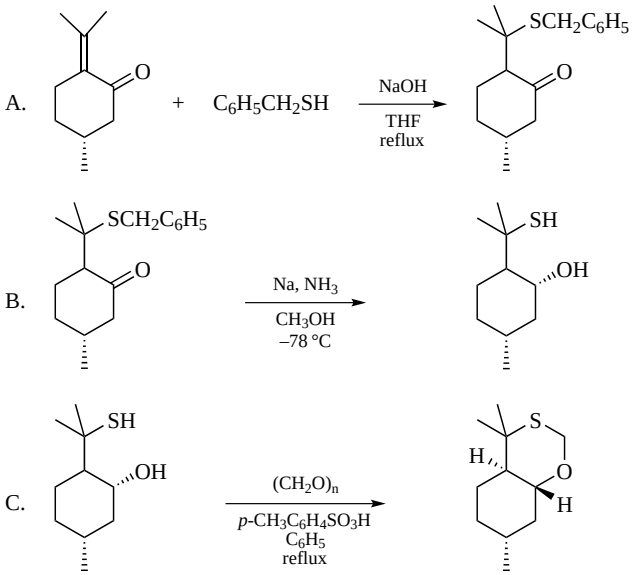
(*S*)-2-[(4*S*)-*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-1,3-oxazolidinyl]-2-*tert*-butyldimethylsiloxyethanal

A. Dondoni and D. Perrone; *Org. Synth.* **2000**, *77*, 78.



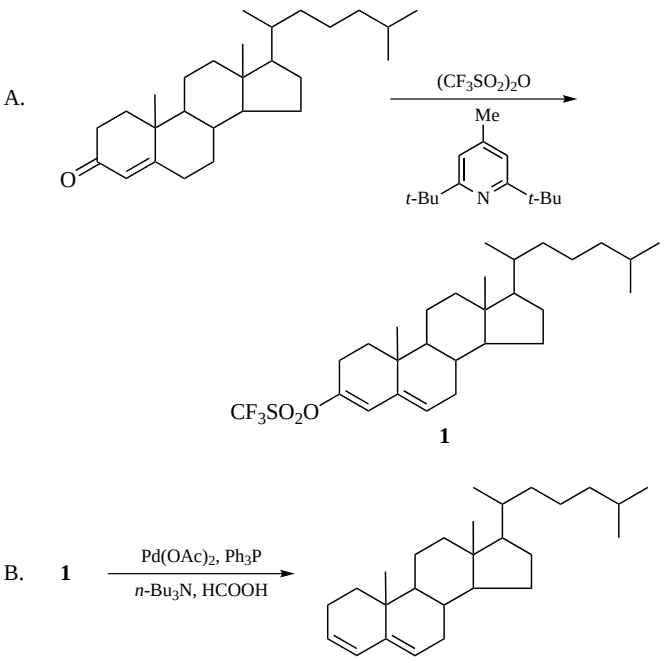
Chiral 1,3-Oxathiane from (+)-Pulegone: Hexahydro-4,4,7-Trimethyl-4*H*-1,3-benzoxathiin

E. L. Eliel, J. E. Lynch, F. Kume, and S. V. Frye; *Org. Synth.* **1987**, *65*, 215.



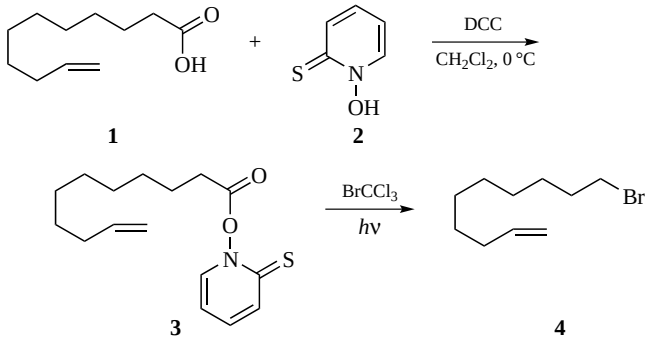
Cholesta-3,5-diene

S. Cacchi, E. Morera, and G. Ortar; *Org. Synth.* **1990**, *68*, 138.



Dec-9-enyl Bromide from 10-Undecenoic Acid

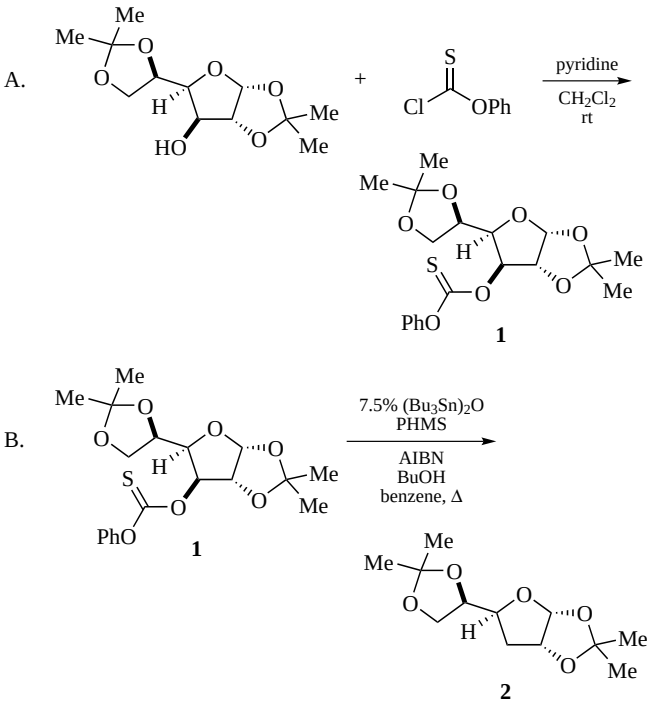
D. H. R. Barton, J. MacKinnon, R. N. Perchel, and C.-L. Tse; *Org. Synth.* **1998**, *75*, 124.



1 **2** **3** **4**

3-Deoxy-1,2:5,6-bis-*O*-(1-methylethylidene)-α-D-ribo-hexofuranose

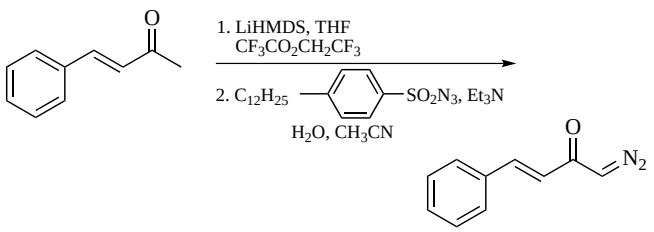
J. Tormo and G. C. Fu; *Org. Synth.* **2002**, *78*, 239.



1 **2**

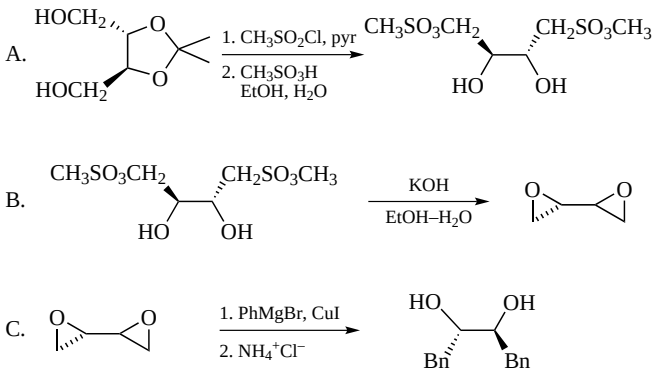
(*E*)-1-Diazo-4-phenyl-3-buten-2-one

R. L. Danheiser, R. F. Miller, and R. G. Brisbois; *Org. Synth.* **1995**, *73*, 134.



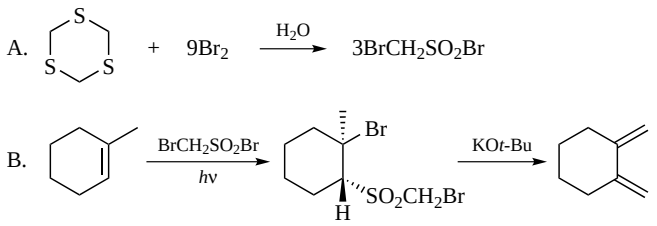
(2*S*,3*S*)-Dihydroxy-1,4-diphenylbutane

M. A. Robbins, P. N. Devine, and T. Oh; *Org. Synth.* **1999**, *76*, 101.



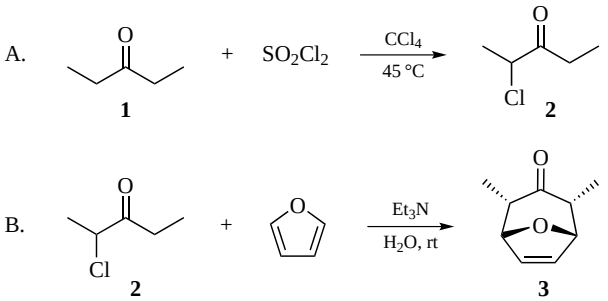
1,2-Dimethylenecyclohexane

E. Block and M. Aslam; *Org. Synth.* **1987**, *65*, 90.



2,4-*endo*,*endo*-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one

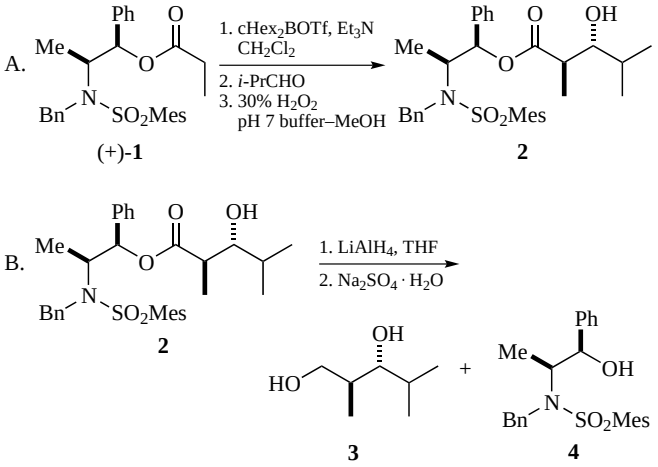
M. Lautens and G. Bouchain; *Org. Synth.* **2003**, *79*, 251.



1 **2** **3**

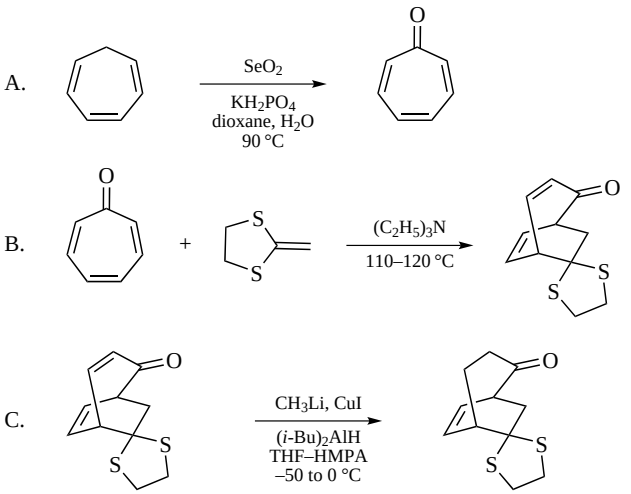
(2*S*,3*R*)-2,4-Dimethyl-1,3-pentanediol

A. Abiko; *Org. Synth.* **2003**, *79*, 116.



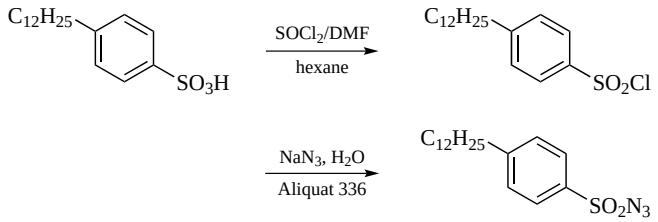
9-Dithiolanobicyclo[3.2.2]non-6-en-2-one

K. R. Dahnke and L. A. Paquette; *Org. Synth.* **1993**, *71*, 181.



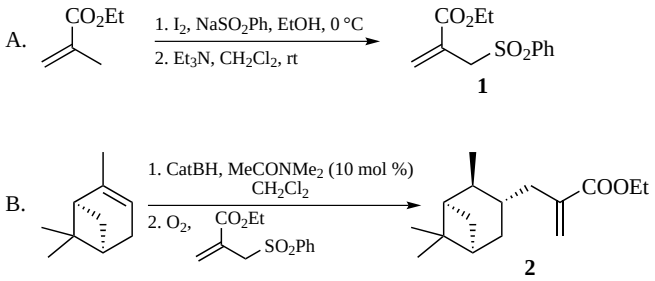
4-Dodecylbenzenesulfonyl Azides

G. G. Hazen, F. W. Bollinger, F. E. Roberts, W. K. Russ, J. J. Seman, and S. Staskiewicz; *Org. Synth.* **1995**, *73*, 144.



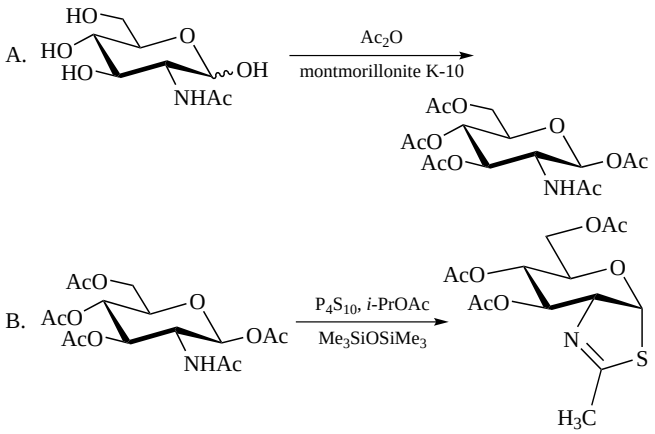
Ethyl 2-{[(1*S*,2*R*,3*R*,5*S*-2,6,6-Trimethylbicyclo[3.1.1]hept-3-yl]methyl}acrylate

V. Darmency, E. M. Scanlan, A. P. Schaffner, and P. Renaud; *Org. Synth.* **2006**, *83*, 24.



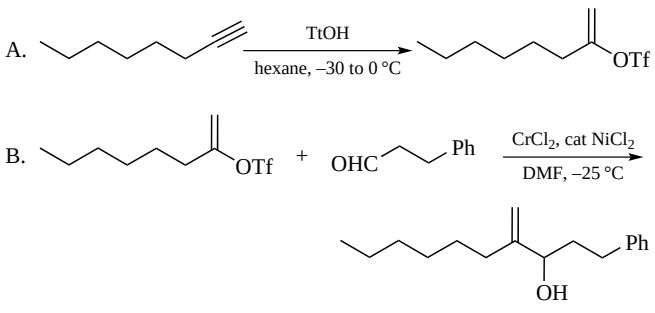
GlcNAc-thiazoline Triacetate

S. Knapp, R. A. Huhn, and B. Amorelli; *Org. Synth.* **2007**, *84*, 68.



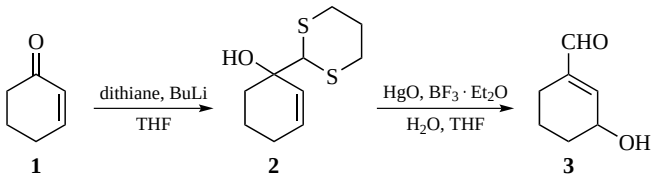
2-Hexyl-5-phenyl-1-penten-3-ol

K. Takai, K. Sakogawa, Y. Kataoka, K. Oshima, and K. Utimoto; *Org. Synth.* **1995**, *72*, 180.



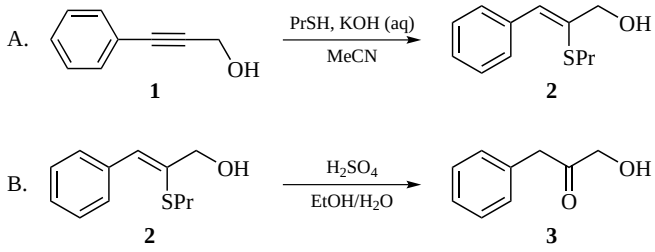
3-Hydroxy-1-cyclohexene-1-carboxaldehyde

H. L. Rigby, M. Neveu, D. Pauley, B. C. Ranu, and T. Hudlicky; *Org. Synth.* **1989**, *67*, 205.



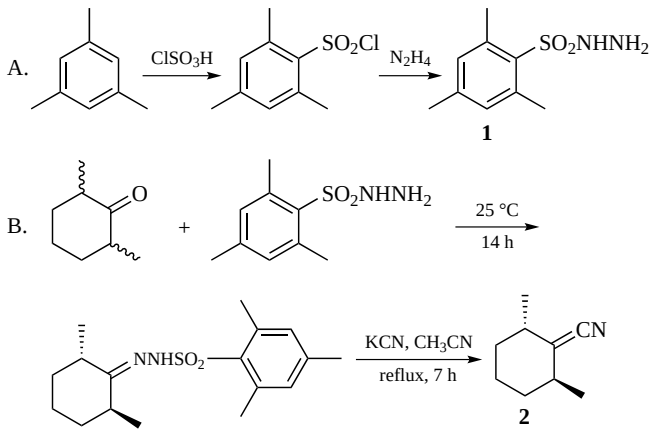
1-Hydroxy-3-phenyl-2-propanone

M. S. Waters, K. Snelgrove, and P. Maligres; *Org. Synth.* **2003**, *80*, 190.



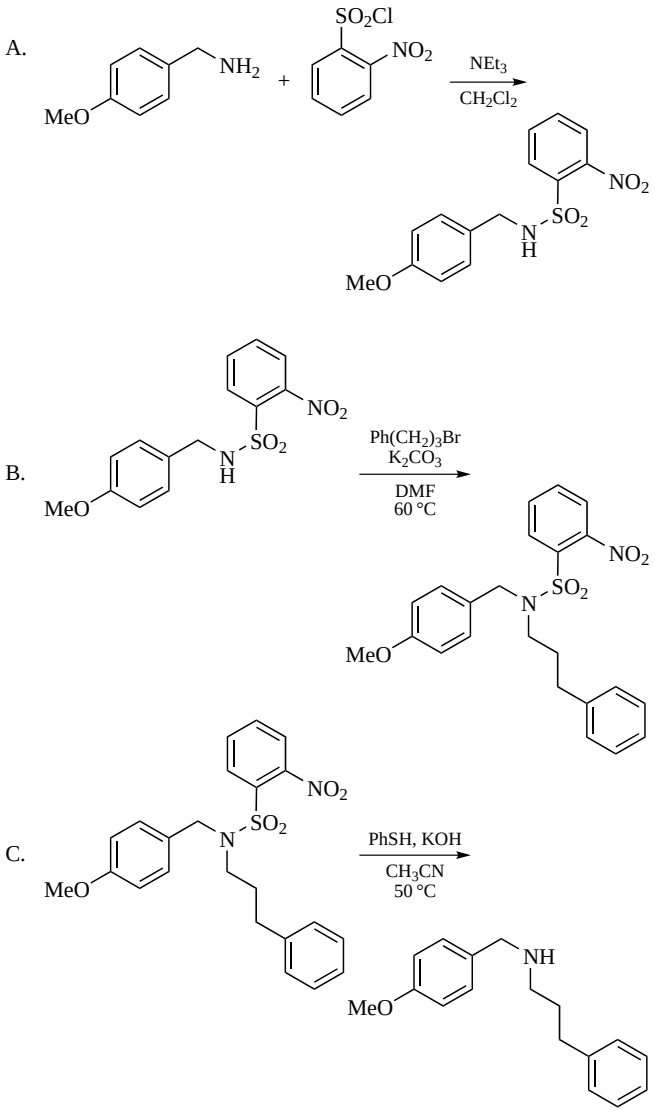
Mesitylenesulfonylhydrazine, and (1α,2α,6β)-2,6-Dimethylcyclohexanecarbonitrile and (1α,2β,6α)-2,6-Dimethylcyclohexanecarbonitrile as a Racemic Mixture

J. R. Reid, R. F. Dufresne, and J. J. Chapman; *Org. Synth.* **1997**, *74*, 217.



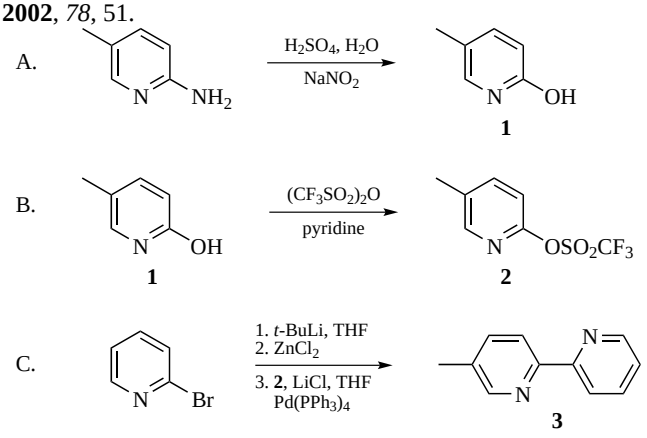
N-(4-Methoxybenzyl)-3-phenylpropylamine

W. Kurosawa, T. Kan, and T. Fukuyama; *Org. Synth.* **2003**, *79*, 186.



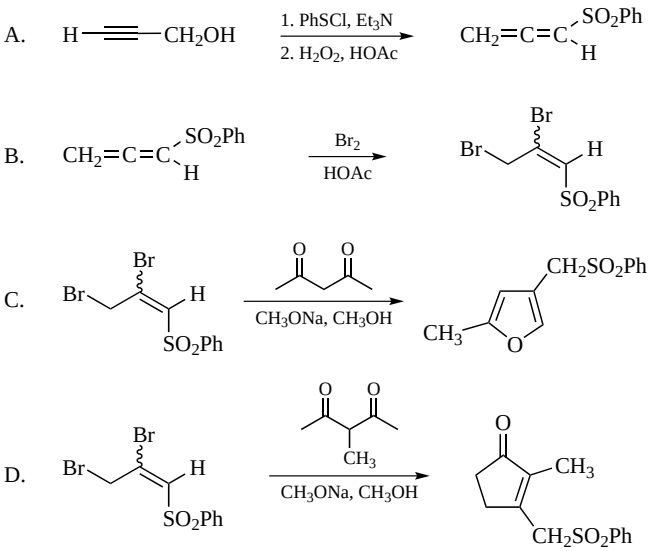
5-Methyl-2,2′-bipyridine

A. P. Smith, S. A. Savage, J. C. Love, and C. L. Fraser; *Org. Synth.* **2002**, *78*, 51.



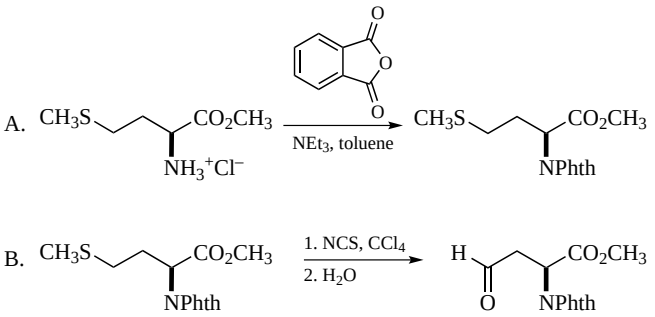
2-Methyl-4-[(phenylsulfonyl)methyl]furan and 2-Methyl-3-[(phenylsulfonyl)methyl]-2-cyclopenten-1-one

S. H. Watterson, Z. Ni, S. S. Murphree, and A. Padwa; *Org. Synth.* **1997**, *74*, 115.



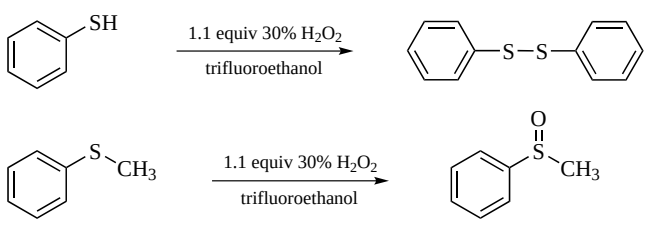
Methyl (*S*)-2-Phthalimido-4-oxobutanoate

P. Meffre, P. Durand, and F. Le Goffic; *Org. Synth.* **1999**, *76*, 123.



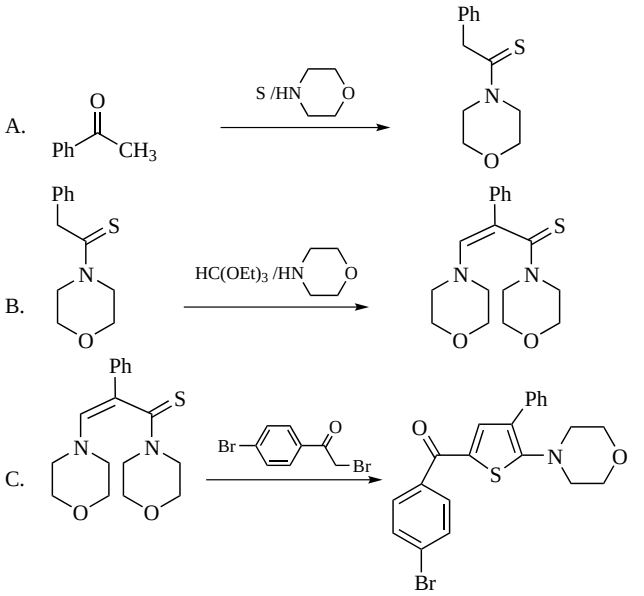
Mild and Selective Oxidation of Sulfur Compounds in Trifluoroethanol: Diphenyl Disulfide and Methyl Phenyl Sulfoxide

K. S. Ravikumar, V. Kesavan, B. Crousse, D. Bonnet-Delpon, and J.-P. Begue; *Org. Synth.* **2003**, *80*, 184.



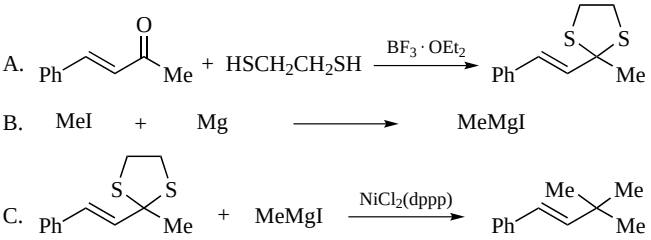
3-Morpholino-2-phenylthioacrylic Acid Morpholide and 5-(4-Bromobenzolyl-2-(4-morpholino)-3-phenylthiophene

A. Rolfs and J. Liebscher; *Org. Synth.* **1997**, *74*, 257.



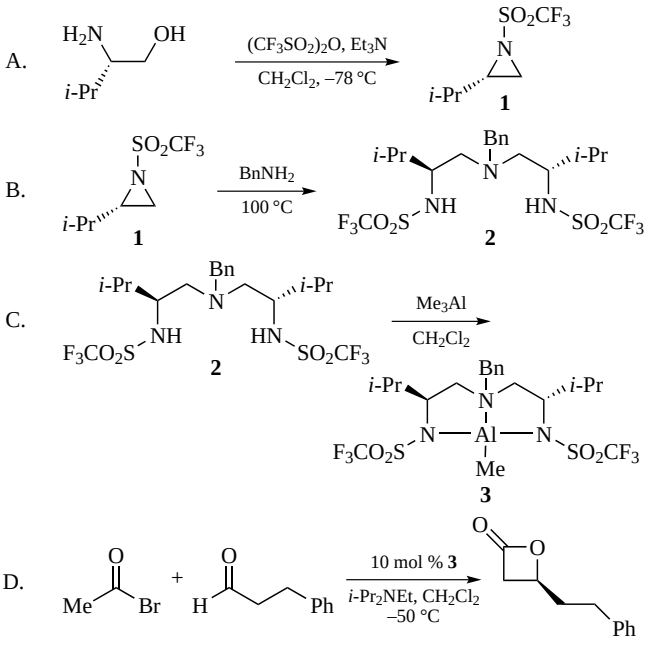
(*E*)-1-Phenyl-3,3-dimethyl-1-butene

T.-M. Yuan and T.-Y. Luh; *Org. Synth.* **1997**, *74*, 187.



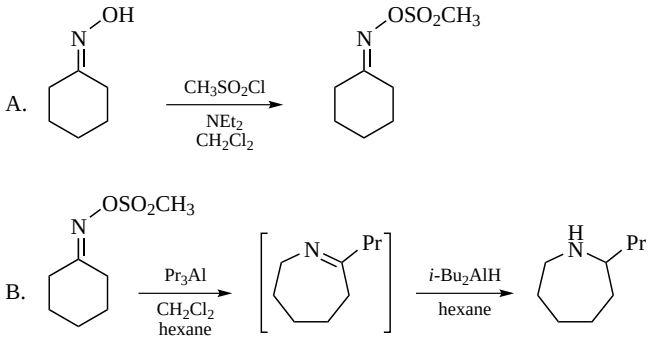
4*S*-4-(2-Phenylethyl)-2-oxetanone

S. G. Nelson and P. M. Mills; *Org. Synth.* **2005**, *82*, 170.



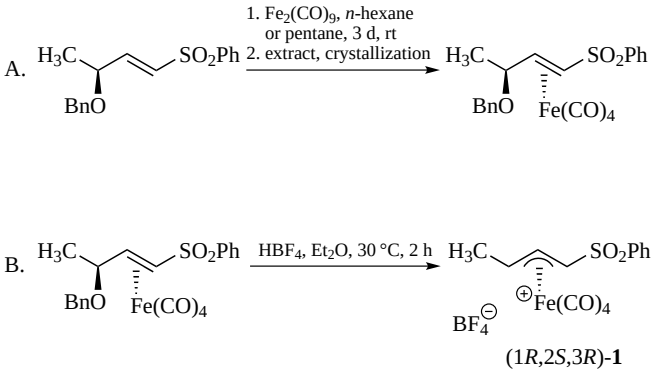
2-Propyl-1-azacycloheptane from Cyclohexanone Oxime

K. Maruoka, S. Nakai, and H. Yamamoto; *Org. Synth.* **1988**, *66*, 185.



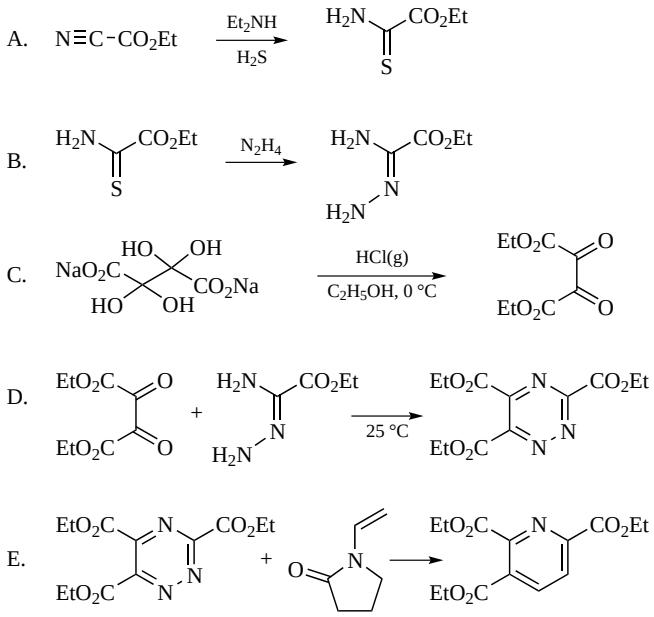
(+)-(1*R*,2*S*,3*R*)-Tetracarbonyl[(1-3η)-1-(phenylsulfonyl)but-2-en-1-yl]iron(1+) Tetrafluoroborate

D. Enders, B. Jandeleit, and S. von Berg; *Org. Synth.* **2002**, *78*, 189.



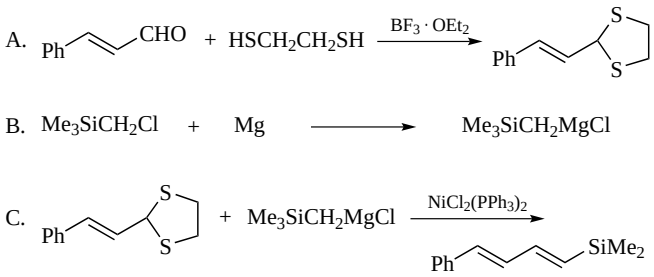
Triethyl 1,2,4-triazine-3,5,6-tricarboxylate

D. L. Boger, J. S. Panek, and M. Yasuda; *Org. Synth.* **1988**, *66*, 142.



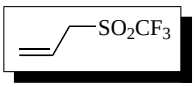
(*E*,*E*)-Trimethyl(4-phenyl-1,3-butadienyl)silane

Z. J. Ni and T.-Y. Luh; *Org. Synth.* **1992**, *70*, 240.



A

Allyl Triflone



[73587-48-1] $C_4H_5F_3O_2S$ (MW 174.14)
InChI = 1/C4H5F3O2S/c1-2-3-10(8,9)4(5,6)7/h2H,1,3H2
InChIKey = QPPGNZFPJHEEHR-UHFFFAOYAB

(allylating agent)

Alternate Names: 3-(trifluoromethylsulfonyl)prop-1-ene; allyl trifluoromethyl sulfone.
Physical Data: bp 171.5 °C.
Form Supplied in: colorless liquid; not commercially available.
Handling, Storage, and Precautions: moisture sensitive; thermally labile.

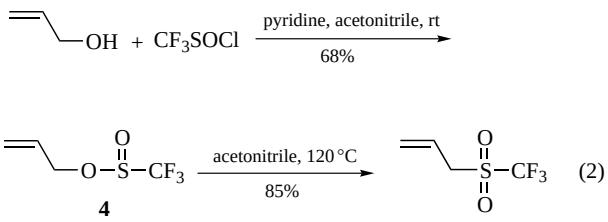
Free-radical allylations are powerful tools for the selective formation of carbon-carbon bonds under mild conditions. These transformations have been accomplished by reacting alkyl halides with allyl stannanes, allyl silanes, allyl sulfones, the title compound allyl trifluoromethanesulfone (allyl triflone), and its substituted derivatives. The strong electron withdrawing ability of the trifluoromethylsulfone group in allyl triflones facilitates the addition of an alkyl radical to an electron deficient triflone. The use of allyl triflones, together with other reagents such as allyl sulfones, avoids the toxicity and difficulty in removing tin residues from the products associated with stannane reagents.

Synthesis of Allyl Triflone. Alkyl triflones are formed in a clean, but slow, displacement reaction by nucleophilic substitution of primary halides by potassium triflinate with iodide catalysis in boiling acetonitrile (eq 1).[1]

$$RCH_2Br + KSO_2CF_3 \xrightarrow{\text{KI, acetonitrile reflux}} RCH_2SO_2CF_3 \quad (1)$$

1 **2** **3**

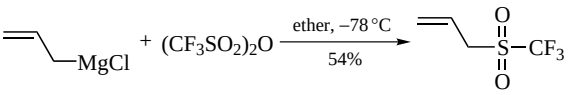
An alternative synthesis of allyl triflones is the triflination of allyl alcohols, which affords triflinates such as **4**, followed by thermal rearrangement in acetonitrile to give allyl triflone (**5**) (eq 2).[2]



(2)

4 **5**

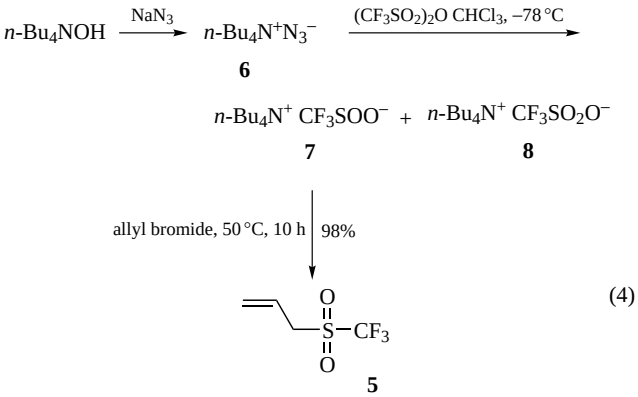
Creary reported the synthesis of allyl triflone in moderate yield by reacting allylmagnesium chloride with triflic anhydride (eq 3).[3]



(3)

5

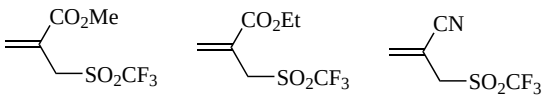
Hendrickson synthesized allyl triflones using tetrabutylammonium triflinate.[4] The quaternary ammonium system is more soluble and 20–40 times more reactive than the conventional potassium triflinate. Tetra-*n*-butylammonium azide (**6**) prepared from tetra-*n*-butylammonium hydroxide and sodium azide reacts with triflic anhydride in chloroform at −78 °C to give a 1:1 mixture of tetrabutylammonium triflinate (**7**) and tetrabutylammonium triflate (**8**). Treatment of this mixture with allyl bromide gives the corresponding allyl triflone (**5**) in almost quantitative yield. The water-soluble triflate coproduct (**8**) in the reaction mixture does not interfere with the formation of (**5**), which is readily isolated (eq 4).



(4)

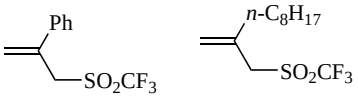
6 **7** **8** **5**

Synthesis of Functionalized Allyl Triflones. The Hendrickson tetrabutylammonium triflinate reagent (**7**/**8**)[4] reported was used by Fuchs and Curran to prepare functionalized allyl triflones (**9**–**13**).[5]



9 **10** **11**

[210489-89-7] [210489-88-6] [210489-90-0]

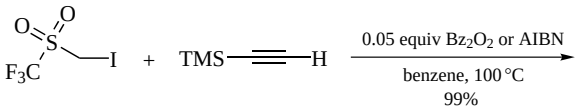


12 **13**

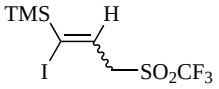
[210489-91-1] [210489-92-2]

Fuchs and co-workers used radical-mediated atom-transfer addition of iodomethyl triflone (**14**) [158530-86-0] to substituted alkynes to afford functionalized allyl triflones.[6] The reaction was complete within 5–10 h in most cases. For example, heating a

benzene solution of iodomethyl triflone (**14**) (1 equiv) and alkyne (2–3 equiv, to ensure an excess of the volatile substrate) in a sealed tube gave allyl triflone (**15**) in 99% yield (eq 5). The procedure was also extended to internal and terminal alkynes. Addition to 1-octyne and 4-octyne proceeded in over 70% yield, but resulted in a mixture of *E*- and *Z*-isomers.



14

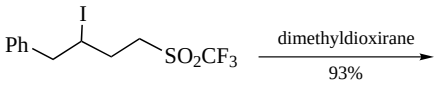


15

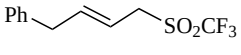
(5)

(*E*:*Z*=1:7.5) *Z*: [162052-46-2] *E*: [162052-45-1]

Fuchs also reported the preparation of allyl triflones through 1,2-elimination of the γ-iodoso triflone intermediate. γ-Iodoso triflone was prepared from γ-iodo triflones using dimethyldioxirane. In all of the cases, the elimination gave the corresponding allyl triflones regio- and stereoselectively (eq 6).[6] Formation of allyl triflone (**17**) demonstrates that the triflone moiety is more inductively activating than the phenyl ring in substrate **16**.



16

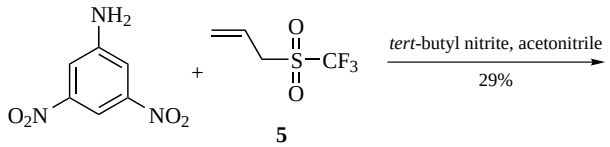


17

(6)

[162052-52-0]

Allyl Triflone as an Allylating Agent. Frejd reported a low yield method using allyl triflone for aromatic allylation through a diazotization/allylation process (eq 7).[7]



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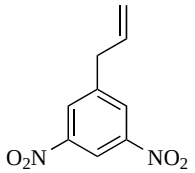
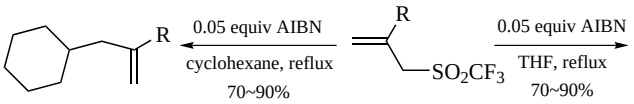
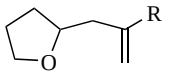


(7)

Curran and Fuchs successfully reacted allyl triflones with THF and cyclohexane to give good to excellent yields of various allyl products through radical-mediated C–H bond functionalization (eq 8).[5]



9a–13a **9–13**



(8)

R = CO_2Me, CO_2Et, CN, Ph, *n*-C_8H_{17} **9b–13b**

1. Hendrickson, J. B.; Giga, A.; Wareing, J., *J. Am. Chem. Soc.* **1974**, *96*, 2275.
2. Hendrickson, J. B.; Skipper, P. L., *Tetrahedron* **1976**, *32*, 1627.
3. Creary, X., *J. Org. Chem.* **1980**, *45*, 2727.
4. Hendrickson, J. B.; Judelson, D. A.; Chancellor, T., *Synthesis* **1984**, 17.
5. Xiang, J.; Evarts, J.; Rivkin, A.; Curran, D. P.; Fuchs, P. L., *Tetrahedron Lett.* **1998**, *39*, 4163.
6. Mahadevan, A.; Fuchs, P. L., *J. Am. Chem. Soc.* **1995**, *117*, 3272.
7. Ek, F.; Wistrand, L.; Frejd, T., *J. Org. Chem.* **2003**, *68*, 1911.

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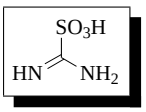
Wyeth Research, Cambridge, MA, USA

Aminoiminomethanesulfonic Acid



[1184-90-3] $CH_4N_2O_3S$ (MW 124.13)

InChI = 1/CH4N2O3S/c2-1(3)7(4,5)6/h(H3,2,3)(H,4,5,6)/f/h2,4H,3H2

InChIKey = AOPRFYAPABFRPU-VAGMHOQLCM

(parent compound and its derivatives guanylate amines; some derivatives give triazoles with azide and aminoiminoethanenitriles with cyanide as nucleophile)

Alternate Name: formamidinesulfonic acid.

Physical Data: mp 131–131.5 °C when highly pure; around 125 °C with dec before purification.

Solubility: sol water; slightly sol methanol, ethanol; insol ether.

Preparative Methods: by the oxidation of thiourea or aminoiminomethanesulfinic acid (formamidinesulfinic acid) with peracetic acid. Many substituted aminoiminomethanesulfonic acids can be prepared in the same way.[1,2] Others have utilized hydrogen peroxide with sodium molybdate as a catalyst to oxidize the corresponding thioureas to a variety of monosubstituted aminoiminomethanesulfonic acids; the substituents include phenyl, 2-methylphenyl, 4-fluorophenyl, *n*-propyl,[3] cyclohexylmethyl, *S*-α-methylbenzyl, cyclooctyl, and benzhydryl.[4]

Purification: recrystallize from glacial acetic acid.

Handling, Storage, and Precautions: stable for at least a few weeks at room temperature. After drying, it remains stable for

at least 5 months if kept in a freezer. Thiourea and its metabolites (probably oxidized thiourea) are tumorigenic and cause lung edema. All direct contact with the compound should be avoided; for example, a dust mask should be worn. All residues should be destroyed with strong bleach solution. Many substituted thioureas and their metabolites are also biologically active. Use in a fume hood.

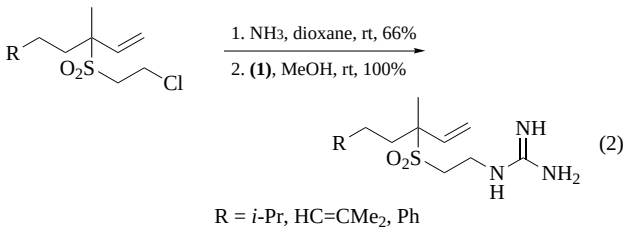
Synthesis of Guanidines from Amines. Aminoiminomethanesulfonic acid (**1**) reacts with a variety of primary amines, including *tert*-butylamine, to give 50–80% yields of the corresponding guanidines (eq 1). This reaction is more facile than guanidine syntheses starting with *S*-alkylisothioureas.[2] Reactions of primary and secondary amines with monosubstituted (phenylamino)- and (*n*-propylamino)iminomethanesulfonic acids also give good to excellent yields of the corresponding guanidines. Treatment of (*n*-propylamino)iminomethanesulfonic acid with a hindered amine, *t*-butylamine, leads to a good yield of the corresponding triazine instead of the guanidine.[3]

(1)

Reaction of aminoiminomethanesulfonic acid with a variety of amino acids gives yields of guanidino acids ranging from 5–80%. Reactions of some amino acids do not lead to an isolable product. Similar results are obtained with (phenylamino)iminomethanesulfonic acid and (phenylamino)-(phenylimino)methanesulfonic acid.[1]

Other Nucleophilic Substitution Reactions. Nucleophilic substitution of a variety of substituted aminoiminomethanesulfonic acids with cyanide leads to the corresponding aminoiminoethanenitriles in 30–87% yield. A number of substituted aminoiminomethanesulfonic acids react with sodium azide in acetic acid to give the corresponding 5-aminotetrazole. This reaction is subject to pronounced steric hindrance. Hydroxylamine and cyanamide also give nucleophilic substitution of the sulfonic acid group.[5]

Agelasidine-A analogs were prepared in two steps by treatment of a chloroethyl sulfone with ammonia followed by aminoiminomethanesulfonic acid (eq 2). Direct displacement of chloride using guanidine furnished the dienyl analog in comparable yield.[6]

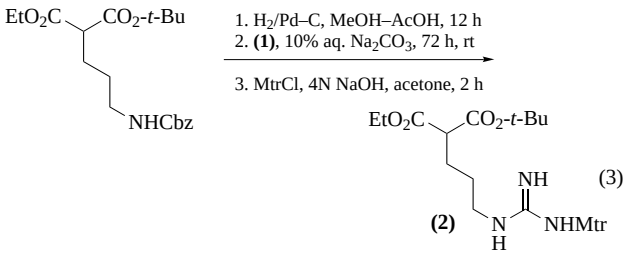


(2)

R = *i*-Pr, HC=CMe$_2$, Ph

Guanylation of 3*R*-methyl-L-arginine with aminoiminomethanesulfonic acid followed by protection with adamantyloxycarbonyl chloride produced the bis-Adoc protected arginine derivative, a key intermediate in the total synthesis of lavendomycin.[7]

In contrast, both (3*R*)- and (3*S*)-hydroxy-L-arginine have been prepared by guanylation of the tridentate copper complexes of *threo*- and *erythro*-2-hydroxy-L-ornithine using *S*-methylisothiourea.[8] Aminoiminomethanesulfonic acid has been used in the synthesis of an α-hydroxy ester *C*-terminal homo-L-arginine tripeptide for evaluation as a thrombin inhibitor.[9] The synthesis of a partially modified retro–inverso T-cell epitope analog required preparation of the malonylarginine intermediate (**2**) using aminoiminomethanesulfonic acid as the guanylating agent (eq 3).[10]

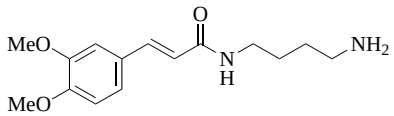


(3)

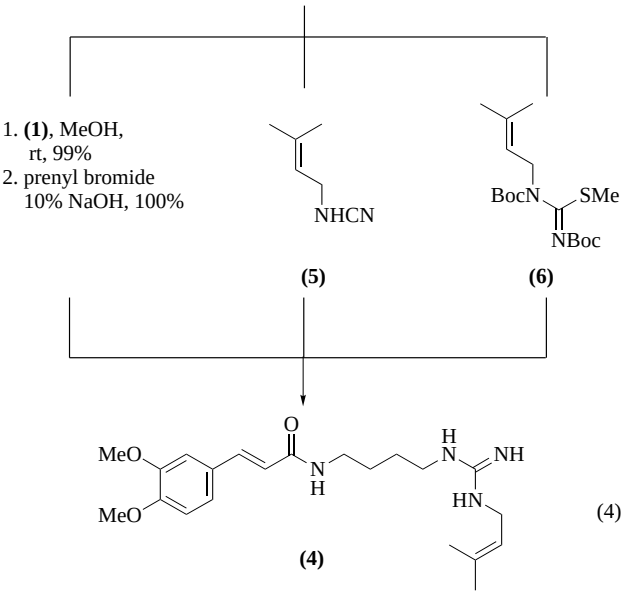
(2)

Mtr = 2,3,6-trimethyl-4-methoxybenzenesulfonyl

Conversion of 3,6-bis(*t*-butyldimethylsilyl)-*N*-(3-aminopropyl) normorphine to the corresponding guanidine analog has been accomplished in high yield using aminoiminomethanesulfonic acid. Interestingly, all attempts to convert the N atom of morphine directly to the analogous guanidine were unsuccessful.[11] Guanylation of the *N*-(4′-aminobutyl)cinnamanilide (**3**) with aminoiminomethanesulfonic acid followed by alkylation with prenyl bromide furnished caracasanamide (**4**) in high yield (eq 4).[12] Alternatively, (**4**) could be prepared by reaction of (**3**) with cyanamide (**5**)[12] or from guanylation using the bis-Boc *S*-methylisothiourea (**6**) followed by cleavage with TFA.[13]



(3)



(4)

(5) **(6)**

(4)

Related Reagents. Cyanamide; Guanidine; *S*-Methylisothiourea; *O*-Methylisourea; 1*H*-Pyrazole-1-carboxamidine Hydrochloride.

1. Miller, A. E.; Bischoff, J. J., *Synthesis* **1986**, 777.
2. Kim, K.; Lin, Y.-T.; Mosher, H. S., *Tetrahedron Lett.* **1988**, *29*, 3183.
3. Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E., *J. Org. Chem.* **1986**, *51*, 1882.
4. Muller, G. W.; Walters, D. E.; Du Bois, G. E., *J. Med. Chem.* **1992**, *35*, 740.
5. Miller, A. E.; Feeney, D. J.; Ma, Y.; Zarcone, L.; Aziz, M. A.; Magnuson, E., *Synth. Commun.* **1990**, *20*, 217.
6. Suryawanshi, S. N.; Rani, A.; Bhakuni, D. S., *Indian J. Chem., Sect. B* **1991**, *30B*, 1089.
7. Schmidt, U.; Mundinger, K.; Mangold, R.; Lieberknecht, A., *J. Chem. Soc., Chem. Commun.* **1990**, 1216.
8. Wityak, J.; Gould, S. J.; Hein, S. J.; Keszler, D. A., *J. Org. Chem.* **1987**, *52*, 2179.
9. Iwanowicz, E. J.; Lin, J.; Roberts, D. G. M.; Michel, I. M.; Seiler, S. M., *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1607.
10. Dürr, H.; Goodman, M.; Jung, G., *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 785.
11. Jackson, W. R.; Copp, F. C.; Cullen, J. D.; Guyett, F. J.; Rae, I. D.; Robinson, A. J.; Pothoulackis, H.; Serelis, A. K.; Wong, M., *Clin. Exp. Pharmacol. Physiol.* **1992**, *19*, 17 (*Chem. Abstr.* **1992**, *117*, 82 892p).
12. Crombie, L.; Jarrett, S. R. M., *J. Chem. Soc., Perkin Trans. 1* **1992**, 3179.
13. Delle Monache, G.; Botta, B.; Delle Monache, F.; Espinal, R.; De Bonnevaux, S. C.; De Luca, C.; Botta, M.; Corelli, F.; Carmignani, M., *J. Med. Chem.* **1993**, *36*, 2956.

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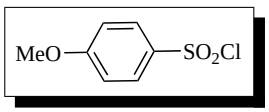
p-Anisolesulfonyl Chloride[1]

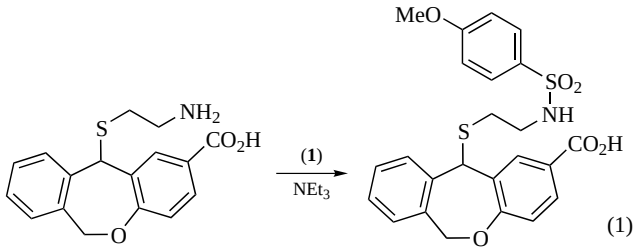


[98-68-0] $C_7H_7ClO_3S$ (MW 206.65)
InChI = 1/C7H7ClO3S/c1-11-6-2-4-7(5-3-6)12(8,9)10/h2-5H, 1H3
InChIKey = DTJVECUKADWGMO-UHFFFAOYAI

(versatile sulfonating agent; useful for the preparation of sulfonamides or as an *N*-protecting group[2])

Alternate Name: 4-methoxybenzenesulfonyl chloride.
Physical Data: mp 40–43 °C.
Solubility: sol acetone, acetonitrile, EtOH, MeOH, dioxane, H_2O.
Form Supplied in: solid; widely available 98% pure.
Handling, Storage, and Precautions: corrosive and a lachrymator. Store at room temperature under anhydrous conditions. Use in a fume hood.

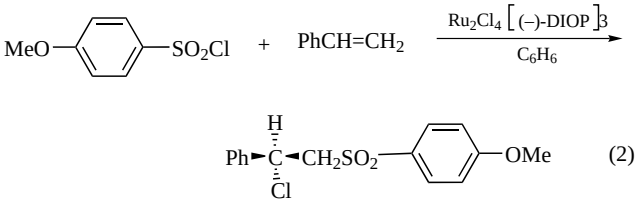
Sulfonating Agent. 4-Methoxybenzenesulfonyl chloride has been employed in the preparation of a wide variety of sulfonamides leading to a number of biologically active compounds.[3,4] The nonprostanoid thromboxane (TXA_2) receptor antagonist (**2**) was prepared from the primary amine in the presence of 4-methoxybenzenesulfonyl chloride (**1**) (1.2 equiv) and excess triethylamine (eq 1).[3] Arenesulfonyl chlorides have also been used for the synthesis of sulfonyl cyanides[5] and arylthiocyanates.[6]



(1)

(**2**)

The addition of sulfonyl chlorides to alkenes in the presence of a catalytic amount of dichlorotris(triphenylphosphine)-ruthenium(II) affords 1:1 adducts.[7] Under these reaction conditions it is believed that sulfonyl radicals, which are confined to the coordination sphere of the metal complex, are involved. When the chiral phosphine (−)-DIOP ((2,3-*O*-isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) is used as a ligand, the addition of 4-methoxybenzenesulfonyl chloride to styrene proceeds to provide the (*R*) isomer in 40% ee (eq 2).[8]



(2)

Arenesulfonyl chlorides have also been cross-coupled in the presence of Pd^0 with both vinyl- and allylstannanes to provide the corresponding sulfones.[9]

Solvolysis of Arenesulfonyl Chlorides. Kinetics on the solvolysis of various arenesulfonyl chlorides indicate an S_N2 mechanism.[10,11]

1. Gordon, I. M.; Maskill, H.; Ruasse, M. F., *Chem. Soc. Rev.* **1989**, *18*, 123.
2. Kitagawa, K.; Kitade, K.; Kiso, Y.; Akita, T.; Funakoshi, S.; Fujii, N.; Yajima, H., *J. Chem. Soc., Chem. Commun.* **1979**, 955.
3. Ohshima, E.; Takami, H.; Sato, H.; Obase, H.; Miki, I.; Ishii, A.; Karasawa, A.; Kubo, K., *J. Med. Chem.* **1992**, *35*, 3394.
4. Brown, T. J.; Chapman, R. F.; Mason, J. S.; Palfreyman, M. N.; Vicker, N.; Walsh, R. J. A., *J. Med. Chem.* **1993**, *36*, 1604.
5. Vrijland, M. S. A., *Org. Synth.* **1977**, *57*, 88.

6. Kagabu, S.; Sawahara, K.; Maehara, M.; Ichihashi, S.; Saito, K., *Chem. Pharm. Bull.* **1991**, *39*, 784.
7. Kamigata, N.; Ozaki, J.; Kobayashi, M., *J. Org. Chem.* **1985**, *50*, 5045.
8. Kameyama, M.; Kamigata, N.; Kobayashi, M., *Chem. Lett.* **1986**, 527.
9. Labadie, S. S., *J. Org. Chem.* **1989**, *54*, 2496.
10. Tonnet, M. L.; Hambly, A. N., *Aust. J. Chem.* **1971**, *24*, 703.
11. Rogne, O., *J. Chem. Soc. (B)* **1968**, 1294.

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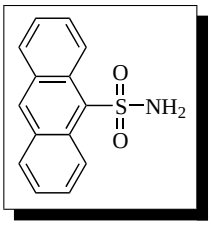
Anthracenesulfonamide



[155495-93-5] $C_{14}H_{11}NO_2S$ (MW 257.31)

InChI = 1/C14H11NO2S/c15-18(16,17)14-12-7-3-1-5-10(12)
9-11-6-2-4-8-13(11)14/h1-9H,(H2,15,16,17)/f/h15H2

InChIKey = FKFZOFZWJNHJDE-YHSKDTNECL

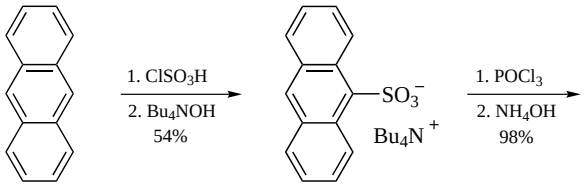
(readily cleavable reagent for the synthesis of β-amino acids and for the iodosulfonamidation of glycals)

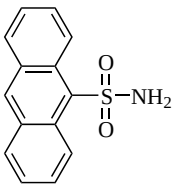
Physical Data: mp 200.5–202.5 °C.

Form Supplied in: yellow solid; synthetically available.

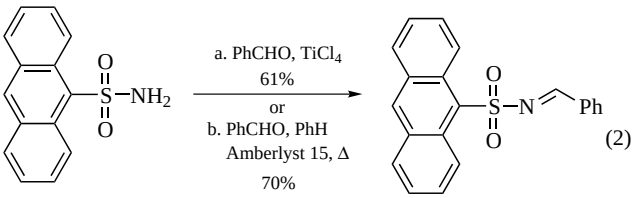
Analysis of Reagent Purity: IR (KBr): $\nu = 3409, 3300, 1312, 1144$ cm^{-1}; ^1H NMR [250 MHz, $(CD_3)_2CO$]: $\delta = 7.0$ (br s, 2H), 7.56–7.72 (m, 4H) 8.19 ('d', $J = 9$ Hz, 2H), 8.91 (s, 1H), 9.37 ('d', $J = 9$ Hz, 2H).

Preparative Methods: synthesized from anthracene by sulfonation with chlorosulfonic acid followed by chlorination with $POCl_3$, then treatment of the crude anthracenesulfonyl chloride with aq NH_3 (eq 1).[1]

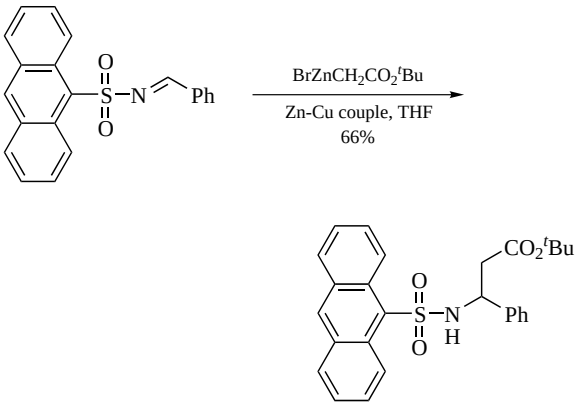



(1)

Synthesis of Protected β-Amino Acids. The synthesis of protected β-amino acids can be accomplished by treatment of an imine, generated by treatment of an aldehyde with anthracenesulfonamide in the presence of either $TiCl_4$ or Amberlyst 15 (eq 2), with $BrZnCH_2CO_2{}^tBu$ in a Reformatsky-like reaction (eq 3).[1]

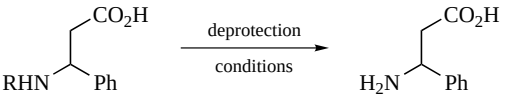


(2)



(3)

The advantage of using anthracenesulfonamide lies in the more facile reductive cleavage of this group compared to other more traditional *N*-sulfonyl protecting groups, such as toluenesulfonamide or 4-methoxycarbonylbenzenesulfonamide (4-MCBS) (eq 4).[1,2]

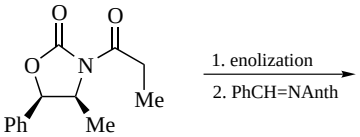


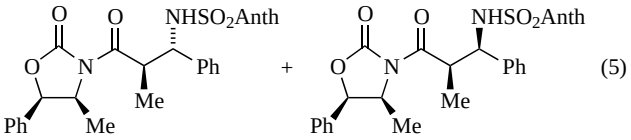
(4)

R	Conditions	Yield (%)
Tosyl	TFA then Na/naphth	11
4-MCBS	TFA then Na/naphth	14
Anthryl	Al/Hg then 1M HCl	63

Optically active β-amino acids have been produced by reaction of the imine generated from anthracenesulfonamide and benzaldehyde using lithium and titanium enolates of *N*-acyloxazolidinones with limited success (eq 5).[3] In this case, however, better results were obtained with the less desirable *N*-tosyl imine (eq 6).

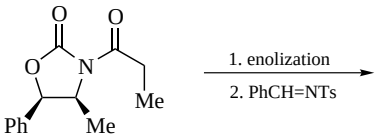
Iodosulfonamidation of Glycals. Anthracenesulfonamide has been used extensively in the iodosulfonamidation of glycals.[4–6] This method involves the *trans*-diaxial addition of *N*-iodoanthracenesulfonamide to a glycal (eq 7). The so-formed iodosulfonamide can then be converted to a 2-α-anthracenoglycosamide derivative by the addition of a nucleophile under the appropriate conditions (eq 8).[7,8]

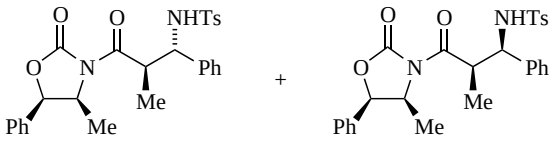




(5)

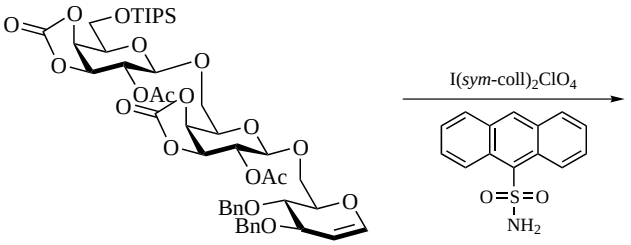
Enolization conditions	Result
LDA, THF	39% Combined yield (unseparable)
$TiCl_4$, EtN^iPr_2	No reaction

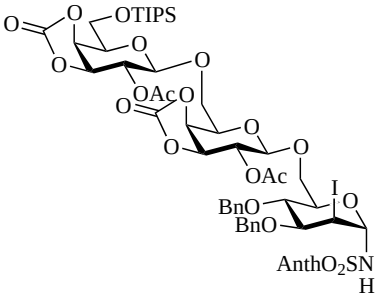




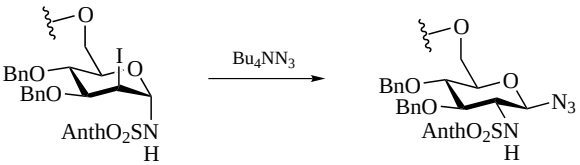
(6)

Enolization conditions	Result
$TiCl_4$, EtN^iPr_2	66% *anti*, 12.5% *syn*



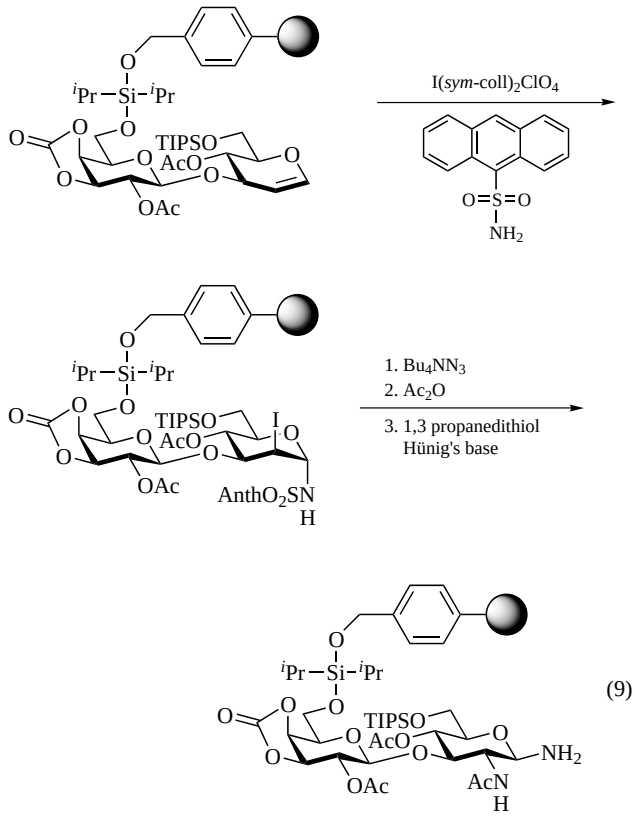


(7)



(8)

The principle advantage to using anthracenesulfonamide, rather than the more widely employed benzenesulfonamide, is that the nitrogen-sulfur linkage can be cleaved under mild conditions, e.g., by thiophenol or 1,3-propanedithiol and Hünig's base. Such mild conditions render this reagent more amenable to solid phase synthesis (eq 9).[9–11] In addition, anthracenesulfonamide is more soluble than benzenesulfonamide in THF, a good swelling solvent for the polymer, resulting in a more efficient and complete reaction.



(9)

Related Reagents. Benzenesulfonamide; Toluenesulfonamide; Mesitylsulfonamide.

1. Robinson, A. J.; Wyatt, P. B., *Tetrahedron* **1993**, *49*, 11329.
2. Arzeno, H. B.; Kemp, D. S., *Synthesis* **1988**, 32.
3. Abrahams, I.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B., *Tetrahedron* **1994**, *50*, 12755.
4. Danishefsky, S. J.; Bilodeau, M. T., *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1381.
5. Arsequell, G.; Valencia, G., *Tetrahedron: Asymmetry* **1999**, *10*, 3045.
6. Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H., *Chem. Rev.* **2000**, *100*, 4495.
7. Danishefsky, S. J.; Roberge, J. Y., *Pure & Appl. Chem.* **1995**, *67*, 1647.
8. Danishefsky, S. J.; Hu, S.; Cirillo, P. F.; Eckhardt, M.; Seeberger, P. H., *Chem. Eur. J.* **1997**, *3*, 1617.
9. Roberge, J. Y.; Beebe, X.; Danishefsky, S. J., *Science* **1995**, *269*, 202.
10. Roberge, J. Y.; Beebe, X.; Danishefsky, S. J., *J. Am. Chem. Soc.* **1998**, *120*, 3915.
11. Savin, K. A.; Woo, J. C. G.; Danishefsky, S. J., *J. Org. Chem.* **1999**, *64*, 4183.

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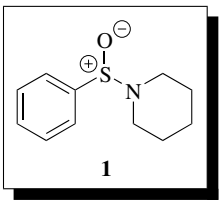
B

1-Benzenesulfinyl Piperidine



1

[4972-31-0] $C_{11}H_{15}NOS$ (MW 209.31)

InChI = 1/C11H15NOS/c13-14(11-7-3-1-4-8-11)12-9-5-2-6-10-12/h1,3-4,7-8H,2,5-6,9-10H2

InChIKey = LBRJCAJLGAXDKP-UHFFFAOYAQ

(reagent used in combination with trifluoromethanesulfonic anhydride to form a powerful electrophilic salt capable of activating thioglycosides and selenoglycosides for the construction of glycosidic linkages; can also be used for the *C*-alkylation of β-ketoester enolates)

Alternate Name: BSP.

Physical Data: mp 84–85 °C.

Solubility: soluble in dichloromethane, diethyl ether, toluene, and most organic solvents.

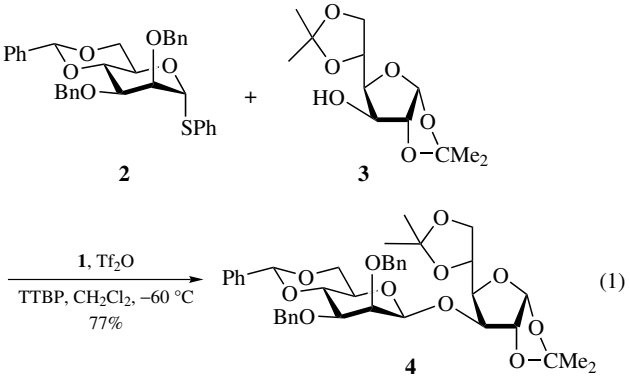
Form Supplied in: off-white solid.

Analysis of Reagent Purity: melting point, NMR spectrum.

Preparative Methods: a solution of PhSOCl (58.0 g, 0.365 mol) in anhydrous diethyl ether (200 mL) is slowly added to a cooled solution (5 °C) of piperidine (72 mL, 0.73 mmol) in anhydrous diethyl ether (200 mL). The reaction mixture is stirred at room temperature for 1 h, filtered, and then concentrated under reduced pressure. The solid residue is triturated with hexanes to give 1-benzenesulfinyl piperidine (53.4 g, 70%).

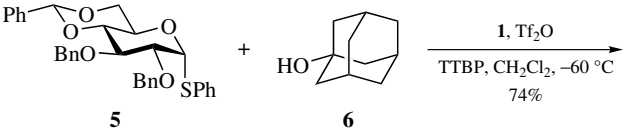
Handling, Storage, and Precaution: unknown toxicity. Should be used within a fumehood.

Activation of Thioglycosides in Glycosylation Reactions.[1] The combination of benzenesulfinyl piperidine (BSP, **1**) and trifluoromethanesulfonic anhydride (Tf_2O) is a powerful tool for the activation of both armed and disarmed thioglycosides in a matter of minutes at low temperature, allowing for the clean conversion to glycosides, upon treatment with alcohols. This reagent combination compares favorably with other methods for the activation of thioglycosides as it allows direct access to otherwise difficult glycosidic linkages such as β-mannosides and α-glucosides in high yield and stereoselectivity. Thus, reaction of thiomannoside (**2**), bearing 4,6-*O*-benzylidene and 2,3-di-*O*-benzyl protecting groups, with **1**/Tf_2O, and the non-nucleophilic base, tri-*tert*-butylpyrimidine (TTBP)[3] reagent combination followed by addition of the glucoside (**3**) provided β-mannoside (**4**) within 5 min in dichloromethane at –60 °C in 77% yield (eq 1). On the other hand, reaction of the thioglucoside (**5**), also bearing the 4,6-*O*-benzylidene and 2,3-di-*O*-benzyl protecting groups, under standard conditions with adamantanol (**6**) provided α-glucoside (**7**) in 74% yield as a single isomer (eq 2).

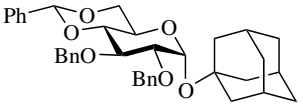


2 **3**

4 (1)

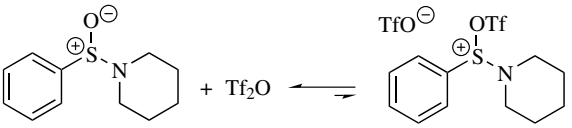


5 **6**

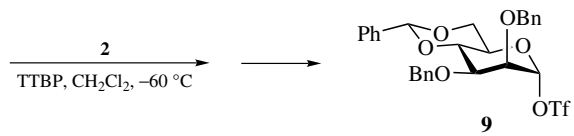


7 (2)

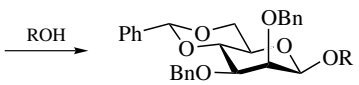
Low temperature studies have determined that the reaction of **1** and Tf_2O is an equilibrium that favors the starting materials over salt **8**. However, salt **8** is a very potent thiophile, capable of converting thioglycosides to glycosyl triflates in a matter of minutes at low temperature. In the presence of thioglycosides, salt **8** is therefore constantly removed from the equilibrium and the reaction is driven to completion. Finally, the thioglycoside reacts with the mannosyl triflate in an S_N2-like manner to give the β-mannoside (eq 3).[1]



1 **8**



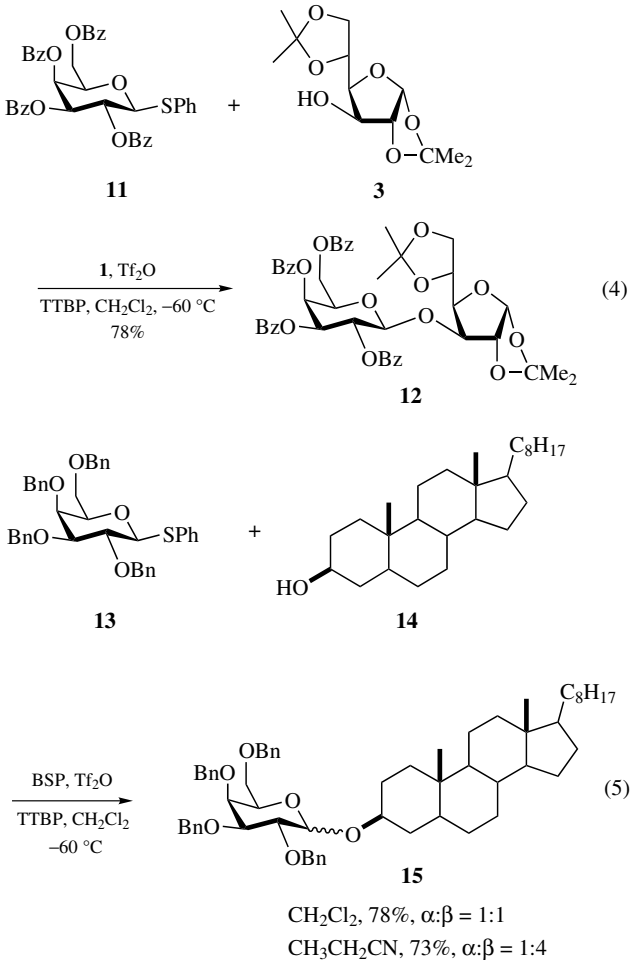
9



10 (3)

The BSP/Tf_2O reagent combination is not limited to the activation of ether protected thioglycosides. It also activates a

wide range of thioglycosides to give standard glycosidic linkages. For example, reaction of tetrabenzoyl thiogalactoside (**11**) under standard conditions, with the glucoside acceptor **3** furnished β-galactoside (**12**) in 78% yield (eq 4).[1] In another example, reaction of tetrabenzyl thiogalactoside (**13**) with 3β-cholestanol (**14**), under standard conditions, provided a 1:1 mixture of α:β-galactoside (**15**) (eq 5). Repeating the reaction mixture in propionitrile as a solvent yielded a 1:4 mixture of the galactoside **15** favoring the β-anomer (eq 5).[1]

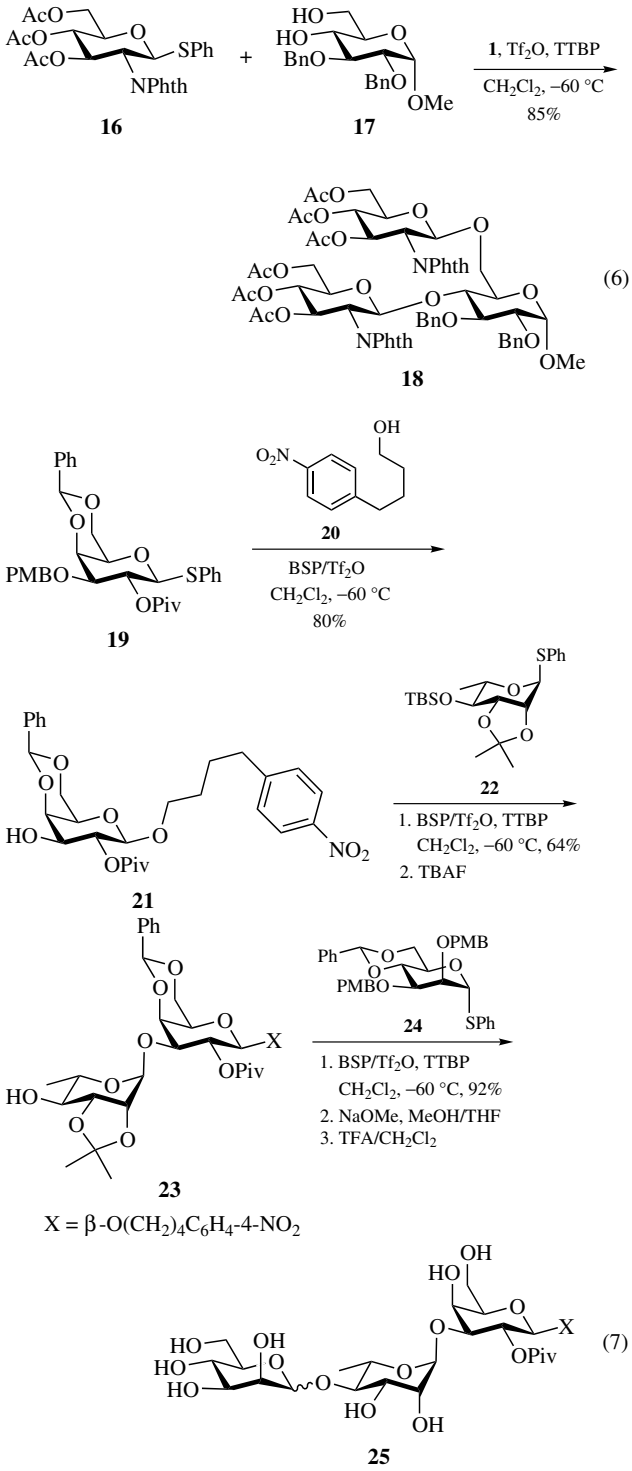


(4)

(5)

The direct synthesis of trisaccharides has also been realized using the standard reagent combination. Thus, treatment of the glucosamine donor **16** with BSP/Tf_2O/TTBP at $-60\,^{\circ}C$ in dichloromethane, followed by addition of 4,6-glucopyranosyl diol (**17**) furnished the trisaccharide **18** in 85% yield as a single isomer (eq 6).[1]

The generality of the BSP/Tf_2O glycosylation method has been displayed in Crich's synthesis of the salmonella type E_1-core trisaccharide (**25**), wherein the three glycosidic bonds were all prepared using this methodology.[4] Thus, reaction of the thiogalactoside (**19**) with BSP/Tf_2O, in the absence of TTBP, with the alcohol **20** provided the thiorhamnoside (**22**) as a single isomer in 80% yield. The acidic conditions of this coupling reaction suppressed any orthoester formation and affected the removal of the PMB protecting group revealing the 3-OH. Treatment of thiorhamnoside (**22**) with the acceptor **21** under standard coupling conditions, followed by deprotection of the silyl group, furnished the disaccharide **23** as a single isomer. Coupling of the acceptor **23** under standard conditions with the thiomannoside donor **24** preceded smoothly in 92% yield as a 9.6:1 mixture favoring the β-anomer. Deprotection with sodium methoxide followed by 5% trifluoroacetic acid provided the desired trisaccharide (**25**) (eq 7).

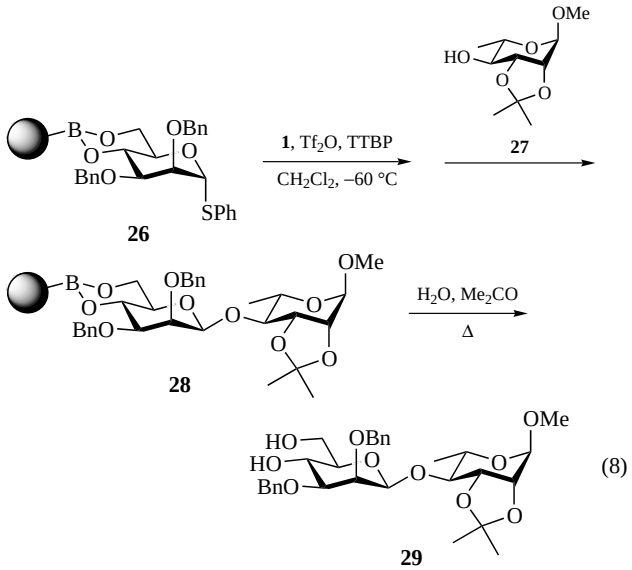


(6)

(7)

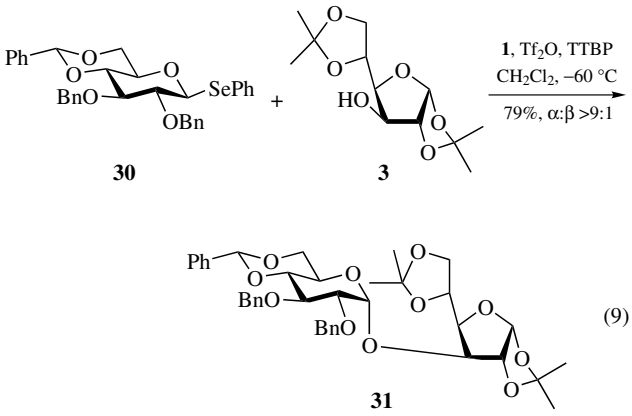
The BSP/Tf_2O methodology has been used in the first example of the direct solid phase synthesis of β-mannosides.[5] Treatment of thiomannoside (**26**), bearing a 4,6-*O*-polystyrylphenylboronate group, with BSP/Tf_2O/TTBP at $-60\,^{\circ}C$ in dichloromethane, followed by the addition of the rhamnosyl acceptor **27** provided

β-mannoside (**28**). The β-mannoside (**29**) was obtained from the resin by heating in acetone and water in 77% overall yield (eq 8). Isolated yields of the β-mannosides from the polymer supported protocol were comparable with those obtained using the analogous solution phase methodology.



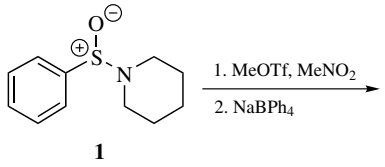
(8)

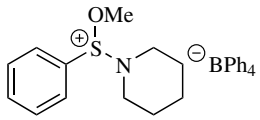
Activation of Selenoglycosides in Glycosylation Reactions.[1] The standard BSP/Tf_2O/TTBP reagent combination activates selenoglycosides in a manner analogous to thioglycosides. Thus, reaction of selenoglycoside (**30**) with the glucosyl acceptor **3** under standard conditions resulted in the isolation of α-glucoside (**31**) in 79% yield as a single isomer (eq 9).[1]



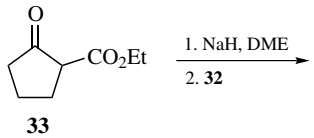
(9)

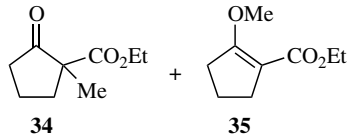
***C*-Alkylation of β-Ketoester Enolates.**[6] Treatment of **1** with MeOTf in $MeNO_2$, followed by anion exchange with sodium tetraphenylborate gave the sulfoxonium salt **32** (eq 10). Reaction of this sulfoxonium salt with the β-ketoester **33** provided a 3:1 mixture favoring the *C*-alkylated product **34** over the *O*-alkylated material **35** (eq 11).[6]





(10)





(11)

3:1

Related Reagents. Benzenesulfenyl Triflate (PhSOTf); *S*-(4-Methoxyphenyl) Benzenethiosulfinate (MPBT).[2]

1. Crich, D.; Smith, M., *J. Am. Chem. Soc.* **2001**, *123*, 9015.
2. Crich, D.; Smith, M., *Org. Lett.* **2000**, *2*, 4067.
3. Crich, D.; Smith, M.; Yao, Q.; Picione, J., *Synthesis* **2001**, 323.
4. Crich, D.; Li, H., *J. Org. Chem.* **2002**, *67*, 4640.
5. Crich, D.; Smith, M., *J. Am. Chem. Soc.* **2002**, *124*, 8867.
6. Pickersgill, I. F.; Marchington, A. P.; Rayner, C. M., *J. Chem. Soc., Chem. Commun.* **1994**, 2597.

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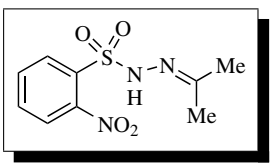
Benzenesulfonic Acid, 2-Nitro-, (1-Methylethylidene)hydrazide



[6655-27-2] $C_9H_{11}N_3O_4S$ (MW 257.27)
InChI = 1/C9H11N3O4S/c1-7(2)10-11-17(15,16)9-6-4-3-5-8(9)12(13)14/h3-6,11H,1-2H3
InChIKey = SBNYNTYNEJTMQO-UHFFFAOYAA

(a reagent used for synthesis of allenes from propargylic alcohols, for the reductive transposition of allylic alcohols and allylic bromides, and for the deoxygenation of unhindered alcohols)

Alternate Names: *N*-isopropylidene *N*′-2-nitrobenzenesulfonyl hydrazine (IPNBSH), isopropylidene *o*-nitrobenzenesulfonylhydrazide.

Physical Data: mp 139–140 °C (dec).

Solubility: soluble in THF, DMSO, 1,4-dioxane, acetone, acetonitrile, and DMF; insoluble in hexanes.

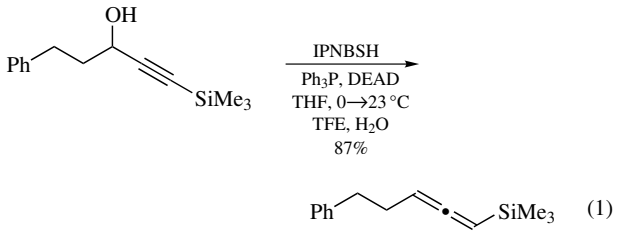
Form Supplied in: white solid.

Preparative Methods: prepared from *o*-nitrobenzenesulfonylhydrazide (NBSH)[1] and acetone at 0 °C.[2] Also commercially available from Sigma–Aldrich.[3]

Purification: a solution of IPNBSH in acetone is diluted with hexanes at 23 °C to induce precipitation.[2,4]

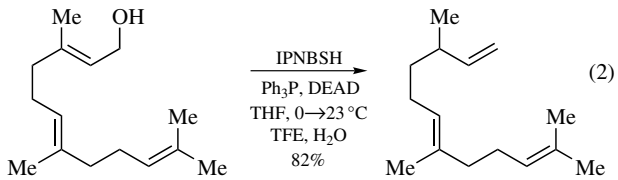
Handling, Storage, and Precaution: stable at ambient temperature for several months.

Synthesis of Allenes.[2] The Mitsunobu displacement of propargylic alcohols with *N*-isopropylidene *N*′-2-nitrobenzenesulfonyl hydrazine (IPNBSH) occurs at room temperature. Dilution of the reaction mixture with a mixture of trifluoroethanol–water (1:1) leads to hydrolysis followed by elimination of 2-nitrobenezenesulfinic acid[5] to afford the corresponding propargylic diazenes.[6] These monoalkyl diazene intermediates[7] undergo spontaneous sigmatropic loss of dinitrogen to provide the corresponding allenes (eq 1).[8,9]

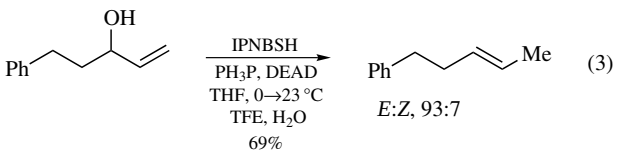


(1)

Reductive Transposition of Allylic Alcohols.[2] Similar to the synthesis of allenes from propargylic alcohols, the Mitsunobu displacement of allylic alcohols with IPNBSH followed by hydrolysis, diazene formation, and sigmatropic loss of dinitrogen provides reductively transposed alkenes. This methodology has proven effective for the reductive transposition of a variety of allylic alcohols (eq 2). The overall transformation provides the desired olefin with high selectivity in the formation of the *trans*-alkene (eq 3).[9h,10]

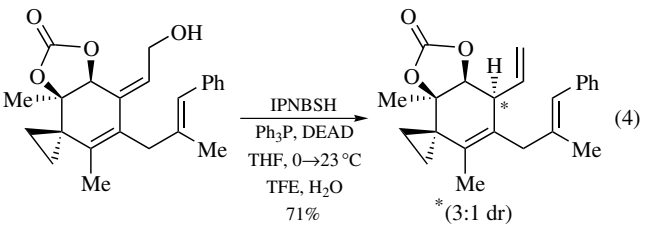


(2)

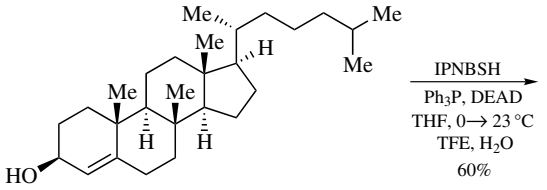


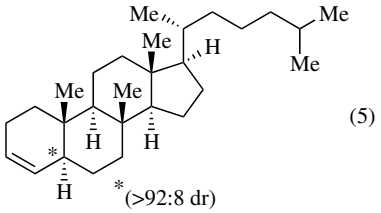
(3)

The mild reaction conditions for the displacement and hydrolysis steps combined with the spontaneous sigmatropic loss of dinitrogen allow the use of this chemistry in complex settings, including conjugated systems, to afford the desired reduction products (eq 4).[11] This chemistry provides the desired reductive transposition products even in recalcitrant substrates for the invertive Mitsunobu displacement reaction (eq 5).



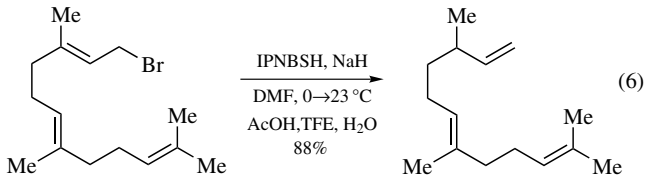
(4)





(5)

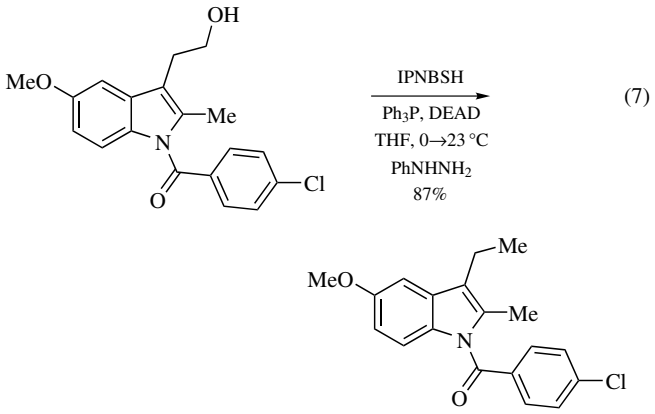
Reductive Transposition of Allylic Halides.[2] Displacement of allylic leaving groups with the sodium sulfonamide of IPNBSH followed by in situ hydrolysis, allylic monoalkyl diazene formation, and sigmatropic loss of dinitrogen affords the reductively transposed product (eq 6).



(6)

Deoxygenation of Unhindered Alcohols.[2] The Mitsunobu displacement of saturated alcohols by IPNBSH followed by an in situ hydrazone exchange reaction with phenylhydrazine and the elimination of 2-nitrobenzenesulfinic acid provides the corresponding monoalkyl diazene intermediates. The saturated monoalkyl diazenes undergo fragmentation and loss of dinitrogen via a free-radical mechanism,[12] and afford the corresponding reduction products (eq 7).

Related Reagents. *o*-Nitrobenzenesulfonylhydrazide; *p*-Toluenesulfonylhydrazide; 2,4-Dinitrobenzenesulfonylhydrazide; Mesitylenesulfonylhydrazide; 2,4,6-Triisopropylbenzenesulfonylhydrazide.



(7)

1. (a) Myers, A. G.; Zheng, B.; Movassaghi, M., *J. Org. Chem.* **1997**, *62*, 7507. (b) Dann, A. T.; Davies, W., *J. Chem. Soc.* **1929**, 1050.
2. Movassaghi, M.; Ahmad, O. K., *J. Org. Chem.* **2007**, *72*, 1838.
3. http://www.sigmaaldrich.com/catalog/search/ProductDetail/ALDRICH/687855.
4. IPNBSH:^{1}H NMR (500 MHz, CD_3CN, 20 °C) δ: 8.25 (br-s, 1H), 8.10–8.06 (m, 1H), 7.86–7.78 (m, 3H), 1.87 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (125.8 MHz, CD_3CN) δ: 160.3, 135.7, 133.6, 133.0, 132.1, 125.9, 120.4, 25.2, 17.7. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): 8.30–8.28 (m, 1H), 7.87–7.85 (m, 2H) 7.79–7.77 (m, 2H), 1.96 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): 159.0, 148.4, 134.3, 133.4, 132.9, 131.9, 125.4, 25.5, 17.1.
5. Hünig, S.; Müller, H. R.; Thier, W., *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271.
6. Myers, A. G.; Finney, N. S., *J. Am. Chem. Soc.* **1990**, *112*, 9641.
7. (a) Kosower, E. M., *Acc. Chem. Res.* **1971**, *4*, 193. (b) Tsuji, T.; Kosower, E. M., *J. Am. Chem. Soc.* **1971**, *93*, 1992.
8. Myers, A. G.; Zheng, B., *J. Am. Chem. Soc.* **1996**, *118*, 4492.
9. For representative use of monoalkyl diazenes in organic synthesis, see: (a) Szmant, H. H.; Harnsberger, H. F.; Butler, T. J.; Barie, W. P., *J. Org. Chem.* **1952**, *74*, 2724. (b) Nickon, A.; Hill, A. S., *J. Am. Chem. Soc.* **1964**, *86*, 1152. (c) Corey, E. J.; Cane, D. E.; Libit, L., *J. Am. Chem. Soc.* **1971**, *93*, 7016. (d) Hutchins, R. O.; Kacher, M.; Rua, L., *J. Org. Chem.* **1975**, *40*, 923. (e) Kabalka, G. W.; Chandler, J. H., *Synth. Commun.* **1979**, *9*, 275. (f) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K., *J. Am. Chem. Soc.* **1987**, *109*, 4717. (g) Myers, A. G.; Finney, N. S.; Kuo, E. Y., *Tetrahedron Lett.* **1989**, *30*, 5747. (h) Myers, A. G.; Kukkola, P. J., *J. Am. Chem. Soc.* **1990**, *112*, 8208. (i) Guziec, F. S., Jr.; Wei, D., *J. Org. Chem.* **1992**, *57*, 3772. (j) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L., *J. Am. Chem. Soc.* **1992**, *114*, 5898. (k) Taber, D. F.; Wang, Y.; Stachel, S. J., *Tetrahedron Lett.* **1993**, *34*, 6209. (l) Bregant, T. M.; Groppe, J.; Little, R. D., *J. Am. Chem. Soc.* **1994**, *116*, 3635. (m) Ott, G. R.; Heathcock, C. H., *Org. Lett.* **1999**, *1*, 1475. (n) Chai, Y.; Vicic, D. A.; McIntosh, M. C., *Org. Lett.* **2003**, *5*, 1039. (o) Sammis, G. M.; Flamme, E. M.; Xie, H.; Ho, D. M.; Sorensen, E. J., *J. Am. Chem. Soc.* **2005**, *127*, 8612.
10. Myers, A. G.; Zheng, B., *Tetrahedron Lett.* **1996**, *37*, 4841.
11. Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G., *Angew. Chem., Int. Ed.* **2006**, *45*, 5859.
12. Myers, A. G.; Movassaghi, M.; Zheng, B., *J. Am. Chem. Soc.* **1997**, *119*, 8572.

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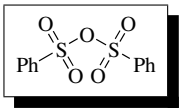
Benzenesulfonic Anhydride



[512-35-6] $C_{12}H_{10}O_5S_2$ (MW 298.33)

InChI = 1/C12H10O5S2/c13-18(14,11-7-3-1-4-8-11)17-19(15,16)12-9-5-2-6-10-12/h1-10H

InChIKey = MLWPJXZKQOPTKZ-UHFFFAOYAF

(mild sulfonating agent; useful for the preparation of sulfonamides, sulfones, and sulfonate esters)

Physical Data: mp 65–80 °C; 88–91 °C after recrystallization from ether.

Solubility: sol diethyl ether, benzene, toluene; insol H_2O.

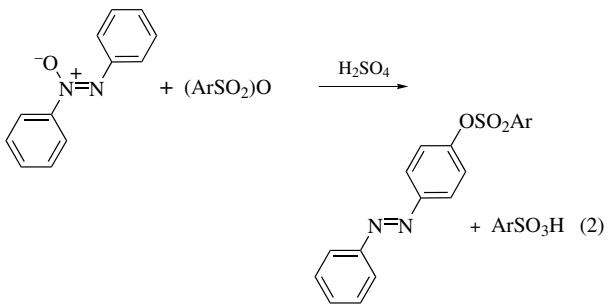
Preparative Methods: prepared on a large scale by heating benzenesulfonic acid with excess phosphorus pentoxide mixed with an inert support.[1] An inert support of 1:1 Supercel kieselguhr and Gooch asbestos was mixed with phosphorus pentoxide and slowly added to benzenesulfonic acid, first at rt then heating to 100 °C. The resultant mixture was heated at 100 °C for 5 h, 1,2-dichloroethane was added, and the solution was refluxed for 10 min. After cooling and successive filtrations, benzenesulfonic anhydride was recovered in 70% yield.

Handling, Storage, and Precautions: the reagent can be stored at rt for extended periods under anhydrous conditions. Liquefication occurs upon exposure to air for 2.5 h. Explosive when mixed with 90–95% H_2O_2.

General Reactions. Arenesulfonic anhydrides have been used as precursors for a variety of substituted sulfones, sulfonate esters, and sulfonamides. The Friedel–Crafts reaction of benzenesulfonic anhydride and benzene in the presence of $AlCl_3$ provided diphenyl sulfone in 99% yield (eq 1).[1] This has proved to be milder and more efficient than the similar reaction using benzenesulfonyl chloride.[1,2]

(1)

Azoxybenzene is known to rearrange in concentrated sulfuric acid to *p*-hydroxyazobenzene.[3] This acid-catalyzed Wallach rearrangement[4] has been extended by using arenesulfonic anhydrides to furnish the corresponding *p*-arenesulfonyloxyazobenzenes in reasonable yields (eq 2).[5]



(2)

Solvolysis of Benzenesulfonic Anhydride. Solvolysis of various arenesulfonic anhydrides in aqueous acetone revealed the reaction mechanism to be S_N2 in accord with established results for similar systems.[6]

1. Lamar, F., *J. Am. Chem. Soc.* **1952**, *74*, 394.
2. Beckurts, O.; Otto, R., *Chem. Ber.* **1878**, *11*, 2066.
3. Wallach, O.; Belli, L., *Chem. Ber.* **1880**, *13*, 525.
4. Shemyakin, M. M.; Agadzharyan, T. E.; Maimind, V. I.; Kundryavtsen, R. V., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1963**, 1339.
5. Oae, S.; Maeda, T., *Tetrahedron* **1972**, *28*, 2127.
6. Christensen, N. H., *Acta Chem. Scand.* **1966**, *20*, 1955.

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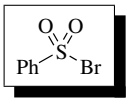
Benzenesulfonyl Bromide

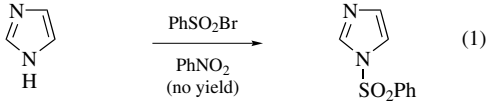


[2297-65-6] $C_6H_5BrO_2S$ (MW 221.07)
InChI = 1/C6H5BrO2S/c7-10(8,9)6-4-2-1-3-5-6/h1-5H
InChIKey = CGWWQPZGKPHLBU-UHFFFAOYAH

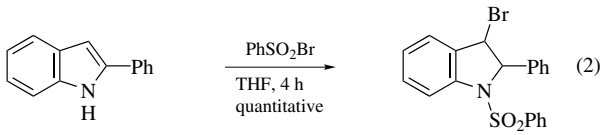
(used as a sulfonating reagent to produce sulfonamides[2–4] and sulfones[5–8])

Physical Data: mp 19.5 °C; bp 76–78 °C/0.17 mmHg.
Solubility: sol CH_2Cl_2, Et_2O, THF, C_6H_6, MeCN.
Preparative Method: prepared by reaction of sodium benzenesulfonate with bromine in 98% yield.[1]
Handling, Storage, and Precautions: by analogy to benzenesulfonyl chloride, benzenesulfonyl bromide should be assumed to be an irritant and harmful by skin absorption and ingestion. Benzenesulfonyl bromide is best used immediately following preparation and may be used in situ. The reagent is moisture sensitive and will react with nucleophilic solvents (e.g. alcohols), liberating HBr and therefore should be stored under an inert atmosphere. Use in a fume hood.

Protection of Nitrogen; Formation of Sulfonamides. Unlike the corresponding arenesulfonyl chlorides, benzenesulfonyl bromide has been used much less extensively in organic synthesis. Primary amines[2] and imidazoles (eq 1)[3] have been converted to the corresponding benzenesulfonamides and, with indoles, bromination at C-3 occurs with concomitant sulfonamide formation (eq 2).[4]

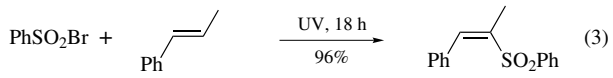


(1)



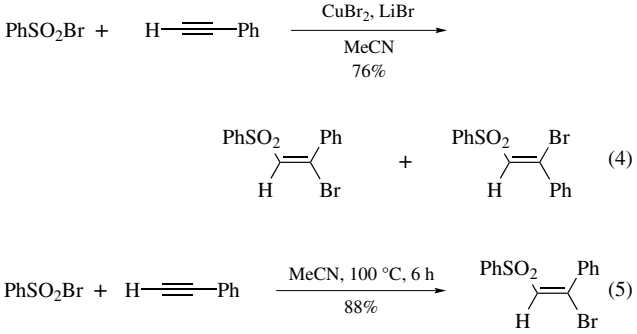
(2)

Addition to Unsaturated Compounds. Benzenesulfonyl bromide undergoes radical-mediated addition to alkenes and alkynes. Addition to alkenes leads to bromo sulfones, which undergo dehydrobromination to give vinyl sulfones (eq 3).[5]



(3)

Addition to vinyl ethers and vinyl esters is regioselective, leading to the corresponding β-alkyloxy/acyloxy sulfone.[6] Addition to alkynes gives vinyl sulfones via a radical pathway. These reactions can be carried out in the presence of peroxide initiators,[7] with Lewis acids such as copper(II) bromide (eq 4),[8] or thermally (eq 5).[8,9]

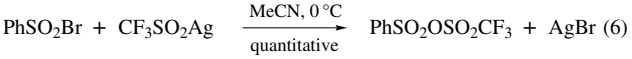


(4)

(5)

With enynes, mixtures of addition products resulting from 1,2- and 1,4-addition have been observed.[10,11] Radical addition with tricyclic alkanes has also been observed.[12]

Reaction with Arenes. Benzenesulfonyl bromide reacts readily with trifluoromethanesulfonyl derivatives, yielding the corresponding mixed anhydrides (eq 6)[13] which have been used to convert arenes to aryl phenyl sulfones under Friedel–Crafts-type conditions.



(6)

1. Cristol, S. J.; Harrington, J. K.; Singer, M. S., *J. Am. Chem. Soc.* **1966**, *88*, 1529.
2. Belousova, I. A.; Savelova, V. A.; Litvinenko, L. M.; Matvienko, V. N., *Zh. Org. Khim.* **1979**, *15*, 1947.
3. Litvinenko, L. M.; Zaslavskii, V. G.; Savelova, V. A.; Dadali, V. A.; Simanenko, Y. S.; Solomoichenko, T. N., *Zh. Org. Khim.* **1976**, *12*, 1945.
4. Dalton, L.; Humphrey, G. L.; Cooper, M. M.; Joule, J. A., *J. Chem. Soc., Perkin Trans. 1* **1983**, 2417.
5. Doomes, E.; Clarke, U.; Neitzel, J., *J. Org. Chem.* **1987**, *52*, 1540.
6. Kalabina, A. V.; Vasil'eva, M. A.; Bychkova, T. I., *Zh. Org. Khim.* **1979**, *15*, 268.

7. Böll, W., *Liebigs Ann. Chem.* **1979**, 1665.
8. Amiel, Y., *J. Org. Chem.* **1974**, *39*, 3867.
9. Pelter, A.; Ward, R. S.; Little, G. M., *J. Chem. Soc., Perkin Trans. 1* **1990**, 2775.
10. Bez "Yazychnaya, L. A.; Stadnichuk, M. D., *Zh. Obshch. Khim.* **1976**, *46*, 1557.
11. Stadnichuk, M. D.; Kryukova, T. B.; Petrov, A. A., *Zh. Obshch. Khim.* **1975**, *45*, 838.
12. Vasin, V. A.; Bolusheva, I. Y.; Chernyaeva, L. A.; Tanaseichuk, B. S.; Surmina, L. S.; Zefirov, N. S., *Zh. Org. Khim.* **1990**, *26*, 1509.
13. Effenberger, F.; Huthmacher, K., *Chem. Ber.* **1976**, *109*, 2315.

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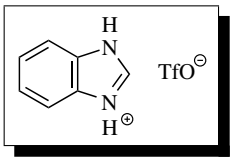
Benzimidazolium Triflate



[99257-95-1] $C_8H_7F_3N_2O_3S$ (MW 268.21)

InChI = 1/C7H6N2.CHF3O3S/c1-2-4-7-6(3-1)8-5-9-7;2-1(3,4)8(5,6)7/h1-5H,(H,8,9);(H,5,6,7)/fC7H7N2.CF3O3S/h8-9H;/q+1;-1

InChIKey = IWYHWZTYVNIDAE-ZJHSAWQHCT

(example of a series of closely related reagents serving as promoters for condensation of a nucleoside phosphoramidite and a nucleoside/nucleotide, constructing internucleotide linkage[1–5])

Physical Data: mp 188–190 °C; density unknown.

Solubility: soluble in H_2O (>0.1 mol/L), methanol (>1 mol/L), and acetonitrile (ca. 0.4 mol/L); insoluble in dichloromethane, ether, and toluene.

Form Supplied in: colorless crystals; not commercially available.

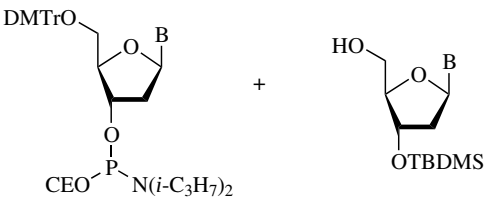
Analysis of Reagent Purity: UV (CH_3OH) λ_{max} 242, 272 nm; ^1H NMR (CD_3OD) 7.53–7.56 (m, 2H), 7.74–7.76 (m, 2H), 9.24 (s, 1H); ^{13}C NMR (CD_3OD) 114.4, 122.4, 127.0, 130.8, 139.8.

Preparative Methods: TfOH (1.0 equiv) is added to benzimidazole (1.0 equiv) in dichloromethane at 0 °C, followed by stirring at 0 °C for 30 min. The precipitated product is collected by filtration.

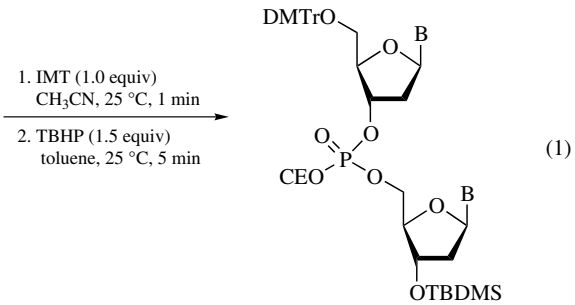
Purity: crystallized from dichloromethane.

Handling, Storage, and Precautions: this reagent is non-hygroscopic and is stable in air. Special care is not necessary during usual handling, but, to keep high quality, store under argon atmosphere. Toxicity unknown.

Synthesis of Nucleotides via the Phosphoramidite Method. Benzimidazolium triflate[1–5] serves as a highly reactive promoter for the condensation of a nucleoside phosphoramidite and a nucleoside (or a nucleotide), which is a key step in the synthesis of oligonucleotides by the phosphoramidite strategy.[6,7] Nucleoside phosphoramidites include 2′-deoxyribonucleoside 3′-phosphoramidites, 2′-deoxyribonucleoside 5′-phosphoramidites, ribonucleoside 2′-phosphoramidites, and ribonucleoside 3′-phosphoramidites. Further, the following benzimidazolium triflate–related compounds also could be used as promoters: imidazolium triflate [mp 197–198 °C; soluble in acetonitrile (>1 mol/L); available from Aldrich],[3,5,8] imidazolium perchlorate [mp >300 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] imidazolium tetrafluoroborate [mp 175–177 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] *N*-methylimidazolium triflate [mp 127–129 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] *N*-phenylimidazolium triflate [mp 126–127 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3–5,9] *N*-phenylimidazolium perchlorate [mp 142–144 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] *N*-phenylimidazolium tetrafluoroborate [mp 96–98 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] *N*-(*p*-acetylphenyl)imidazolium triflate [mp 129–131 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] 2-phenylimidazolium triflate [mp 106–107 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] 4-methylimidazolium triflate [mp 92–93 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] 4-phenylimidazolium triflate [mp 168–169 °C; soluble in acetonitrile (>1 mol/L); not commercially available],[3] benzimidazolium tetrafluoroborate [mp 168–170 °C; soluble in acetonitrile (ca. 0.5 mol/L); not commercially available],[3] and *N*-methylbenzimidazolium triflate [mp 129–130 °C; soluble in acetonitrile (ca. 0.5 mol/L); not commercially available].[3]



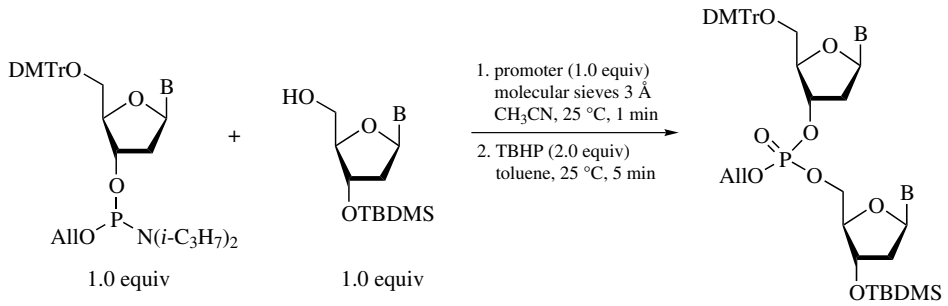
B = *N*-unprotected nucleobase;
CE = $NCCH_2CH_2$;
DMTr = $C_6H_5(p\text{-}CH_3OC_6H_4)_2C$;
IMT = imidazolium triflate



(1)

O-selectivity: 100%

In general, condensation is smoothly achieved and the subsequent oxidation provides a nucleotide in a high yield.



All = $CH_2{=}CHCH_2$;
B = protected nucleobase;
DMTr = $C_6H_5(p\text{-}CH_3OC_6H_4)_2C$

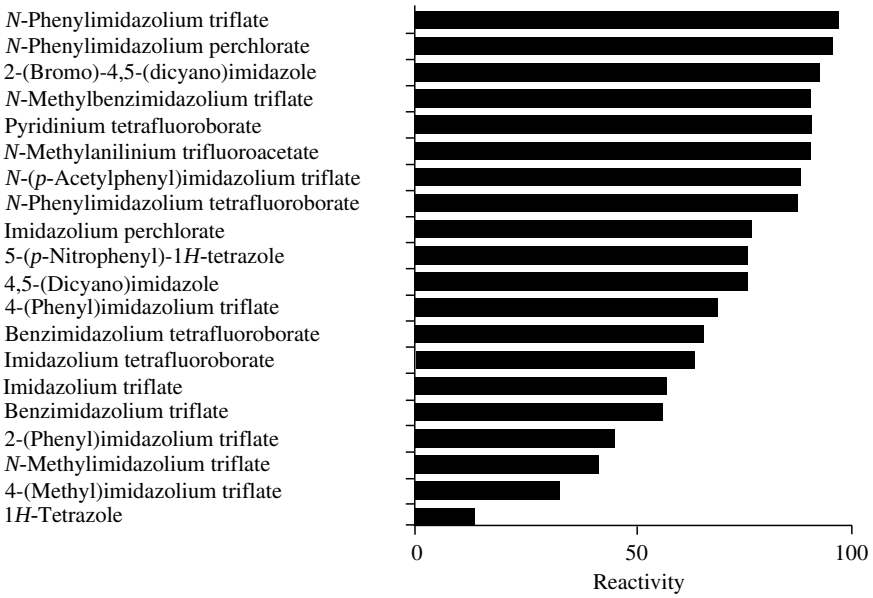


Figure 1 Reactivity of promoters estimated by product yield (^{31}P-NMR assay) obtained by the condensation of a nucleoside phosphoramidite (B = Thy) and a nucleoside (B = Thy) using equimolar amounts (0.02 mmol) of these reactants and the promoter in a 0.02 M acetonitrile solution (25 °C, 1 min), followed by TBHP oxidation (25 °C, 5 min).

For example, the condensation of 2′-deoxyribonucleoside 3′-phosphoramidite and 5′-*O*-free 2′-deoxyribonucleoside promoted by *N*-phenylimidazolium triflate, which is the most reactive among benzimidazolium triflate-related compounds, in a 0.02 M acetonitrile solution is completed in 1–10 min (1–5 min for allyl phosphoramidites; 3–10 min for 2-cyanoethyl phosphoramidites).[3] The reaction using other imidazolium promoters with less reactivity than *N*-phenylimidazolium triflate requires a longer period, usually 10-20 min, for completion. The subsequent oxidation with TBHP[10] gives a dinucleoside phosphate in an almost quantitative yield; bis(trimethylsilyl) peroxide (TMSOOTMS) in the presence of a catalytic amount of TMSOTf[10,11] or 2-butanone peroxide[12] can also be used for this oxidation. Similar results are observed with ribonucleoside 2′- or 3′-phosphoramidites, leading to the construction of 2′–5′- or 3′–5′-inter-ribonucleotidic linkages, respectively. The reaction using these ribonucleoside phosphoramidites is slightly slower than that of 2′-deoxyribonucleoside phosphoramidites. For example, the reaction using ribonucleoside 3′-(allyl phosphoramidite) in a 0.1 M acetonitrile solution requires 5–15 min for completion, even when *N*-phenylimidazolium triflate is used as the promoter.[3] Figures 1 and 2 indicate the relative reactivity of benzimidazolium triflate–related promoters and representative alternative promoters[7,13–19] in the solution-phase preparation of a dideoxyribonucleoside phosphate and a diribonucleoside phosphate, respectively. The imidazolium reagents with high reactivity, such as phenylimidazolium triflate and benzimidazolium triflate, are particularly useful for the synthesis of nucleic acid–related compounds using a phosphoramidite with low reactivity as the building block.[2,3] The approach using imidazolium promoters can be applied to the solid-phase synthesis of oligodeoxyribonucleotides and oligoribonucleotides.

Further, it is noteworthy that imidazolium triflate allows *O*-selective condensation of a nucleoside and a nucleoside phosphoramidite without protection of the nucleobase (eq 1).[5,7]

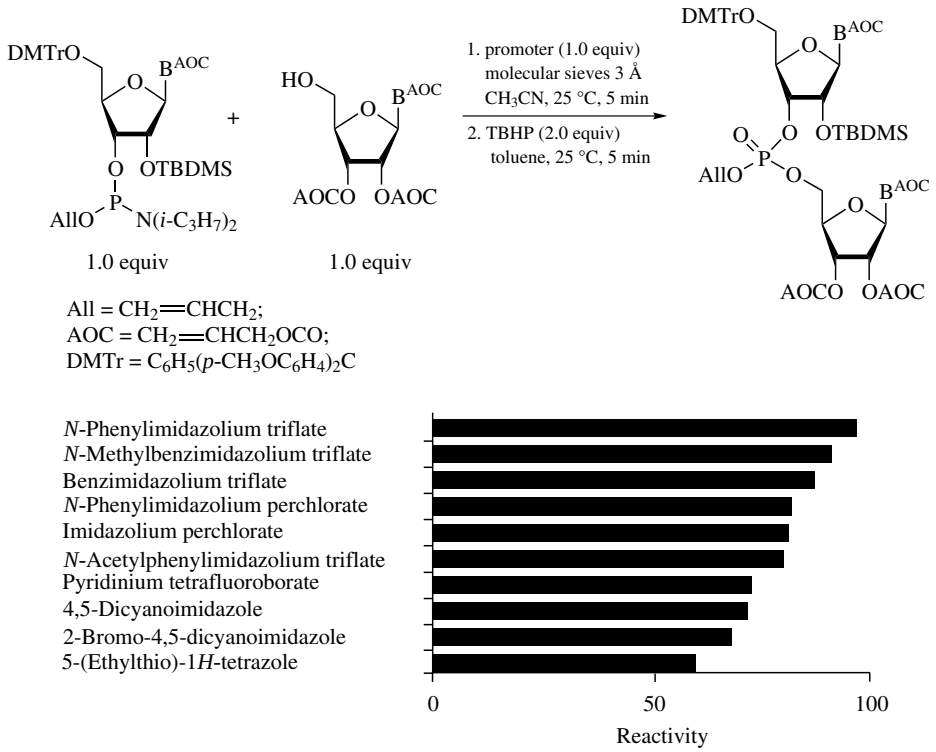


Figure 2 Reactivity of promoters estimated by product yield (^{31}P-NMR assay) obtained by the condensation of a nucleoside phosphoramidite (B = Cyt^{AOC}) and a nucleoside (B = Ade^{AOC}) by the stoichiometric (0.02 mmol each) use of these reactants and the promoter in a 0.1 M acetonitrile solution (25 °C, 5 min), followed by TBHP oxidation (25 °C, 5 min).

1. (a) Hayakawa, Y.; Kataoka, M.; Noyori, R., *J. Org. Chem.* **1996**, *61*, 7996. (b) Sakakura, A.; Hayakawa, Y., *Tetrahedron* **2000**, *56*, 4427.
2. (a) Iwai, S.; Mizukoshi, T.; Fujisawa, Y.; Matsutani, C.; Hanaoka, F.; Hayakawa, Y., *Nucleic Acids Res.* **1999**, *27*, 2299. (b) Matsuura, K.; Hibino, M.; Kataoka, M.; Hayakawa, Y.; Kobayashi, K., *Tetrahedron Lett.* **2000**, *41*, 7529.
3. Hayakawa, Y.; Kawai, R.; Hirata, A.; Sugimoto, J.; Kataoka, M.; Sakakura, A.; Hirose, M.; Noyori, R., *J. Am. Chem. Soc.* **2001**, *123*, 8165.
4. Hayakawa, Y.; Hirata, A.; Sugimoto, J.; Kawai, R.; Sakakura, A.; Kataoka, M., *Tetrahedron* **2001**, *57*, 8823.
5. Hayakawa, Y., *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1547.
6. A comprehensive review: Beaucage, S. L.; Iyer, R. P., *Tetrahedron* **1992**, *48*, 2223.
7. Matteucci, M. D.; Caruthers, M. H., *J. Am. Chem. Soc.* **1981**, *103*, 3185.
8. Hayakawa, Y.; Kataoka, M., *J. Am. Chem. Soc.* **1998**, *120*, 12395.
9. Kawai, R.; Sugimoto, J.; Kataoka, M.; Hayakawa, Y., *Nucleosides, Nucleotides, and Nucleic Acids* **2001**, *20*, 1047.
10. Hayakawa, Y.; Uchiyama, M.; Noyori, R., *Tetrahedron Lett.* **1986**, *27*, 4191.
11. Hayakawa, Y.; Uchiyama, M.; Noyori, R., *Tetrahedron Lett.* **1986**, *27*, 4195.
12. Kataoka, M.; Hattori, A.; Okino, S.; Hyodo, M.; Asano, M.; Kawai, R.; Hayakawa, Y., *Org. Lett.* **2001**, *3*, 815.
13. Beaucage, S. L.; Caruthers, M. H., *Tetrahedron Lett.* **1981**, *22*, 1859.
14. Froehler, B. C.; Matteucci, M. D., *Tetrahedron Lett.* **1983**, *24*, 3171.
15. Vinayak, R.; Colonna, F.; Tsou, D.; Mullah, B.; Andrus, A.; Sproat, B., *Nucleic Acids Symp. Ser.* **1994**, *31*, 165.
16. Fourrey, J.–L.; Varrene, J., *Tetrahedron Lett.* **1984**, *25*, 4511.
17. Brill, W. K.-D., Nielsen, J.; Caruthers, M. H., *J. Am. Chem. Soc.* **1991**, *113*, 3972.
18. Vergeese, C.; Carter, J.; Yegge, J.; Krivjansky, S.; Settle, A.; Kropp, E.; Peterson, K.; Pieken, W., *Nucleic Acids Res.* **1998**, *26*, 1046.
19. Jin, Y.; Just, G., *J. Org. Chem.* **1998**, *63*, 3647.

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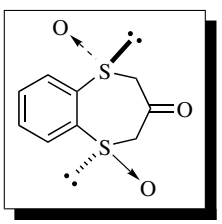
(1*R*,5*R*)-2*H*-1,5-Benzodithiepin-3(4*H*)-one 1,5-Dioxide



[183595-53-1] $C_9H_8O_3S_2$ (MW 228.29)

InChI = 1/C9H8O3S2/c10-7-5-13(11)8-3-1-2-4-9(8)14(12)6-7/h1-4H,5-6H2

InChIKey = ZKBLWRRLZIMWNI-UHFFFAOYAP

(chiral auxiliary for asymmetric desymmetrization of cyclic *meso*-1,2-diols)

Alternate Names: 2*H*-1,5-benzodithiepin-3(4*H*)-one, 1,5-dioxide, (1*R-trans*)-; (1*R*,5*R*)-1,5-benzodithiepan-3-one 1,5-dioxide.

Physical Data: colorless prisms, mp 195.0–196.0 °C (decomposes) (from hexane/EtOAc), $[\alpha]_D^{25}$ −100.3 (*c* 0.29, $CHCl_3$).

Solubility: soluble in MeOH, acetone, EtOAc, THF, CH_2Cl_2, and $CHCl_3$.

Form Supplied in: colorless powder; not commercially available.

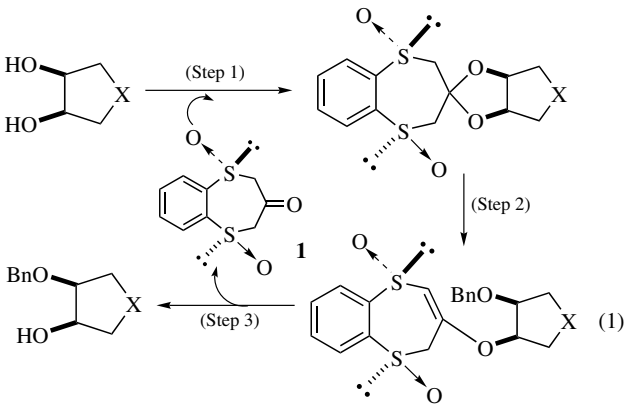
Analysis of Reagent Purity: ^1H and ^{13}C NMR; elemental analysis.

Preparative Methods: the title reagent can be prepared from commercially available (1,2-benzenedithiol[1] and 1,3-dichloroacetone. After condensation of these reagents in the presence of DMAP, the resulting 1,5-benzodithepan-3-one is enantioselectively oxidized to the (*R*)-monosulfoxide by modified Sharpless oxidation [cumene hydroperoxide, Ti(O-*i*-Pr)$_4$] in the presence of (+)-diethyl tartrate as a chiral ligand.[2,3] Subsequent dry ozonation[4] of the (*R*)-monosulfoxide affords (1*R*,5*R*)-bis-sulfoxide **1**, having >98% optical purity. Alternative use of (−)-diethyl tartrate in the modified Sharpless oxidation makes possible convenient access to enantiomeric (1*S*,5*S*)-**1**.[5,6]

Purity: purification is performed by column chromatography. Since unpurified (1*R*,5*R*)-bis-sulfoxide **1** is only slightly soluble in the eluent, the following procedure is convenient. The crude material is dissolved in EtOAc and mixed with silica gel (ca. 5 g silica gel per 1 g of crude reagent). After solvent evaporation, the silica gel residue containing **1** is added to the top of the column and eluted with hexane–EtOAc (2:1).

Handling, Storage, and Precautions: the reagent can be stored for at least 1 month at room temperature without loss of its chemical and optical purities.

Introduction. (1*R*,5*R*)-2*H*-1,5-Benzodithiepin-3(4*H*)-one 1,5-dioxide (C_2-symmetric bis-sulfoxide **1**) has been used as a chiral auxiliary for asymmetric desymmetrization of cyclic *meso*-1,2-diols via diastereoselective acetal cleavage reaction. The procedure consists of three steps (eq 1), that is, acetalization (step 1), acetal cleavage reaction followed by benzylation (step 2), and hydrolysis of the vinyl ether (step 3). Due to the C_2-symmetry of **1**, the chiral auxiliary gives only one product in step 1. In addition, no regio- or geometric isomers of the enol ether are formed in step 2. This reagent can be recovered by acid-promoted hydrolysis and reused.



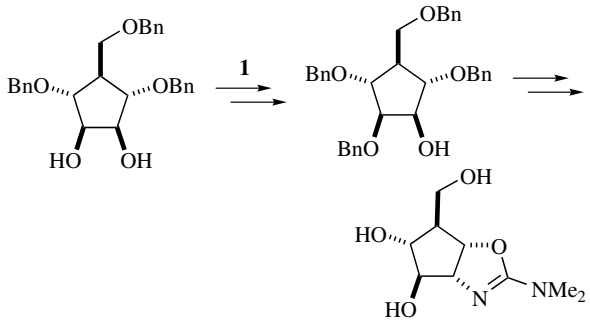
(1)

Acetal Formation Involving C_2-Symmetric Bis-sulfoxide and *meso*-1,2-Diols (Step 1). Acetalization of *meso*-1,2-diols with this reagent should be conducted with TMSOTf and 2,6-lutidine in dichloromethane below 4 °C.[7] Higher temperatures and prolonged reaction times cause undesirable racemization and decomposition of the reagent. When the reactivity of *meso*-1,2-diols with the chiral auxiliary is low, acetalization using the mono-TMS ether of *meso*-diols and TMSOTf is recommended.[8]

Diastereoselective Acetal Fission Followed by Benzylation (Step 2). Upon treatment with KHMDS and 18-crown-6 in THF at −78 °C, the acetal from the (*R*,*R*)-bis-sulfoxide is rapidly converted into the alkoxide having the (1*S*,2*R*) configuration. The counter cation of the base is very important for high selectivity. Diastereoselectivity was seen to increase in the order LiHMDS (8% de) <NaHMDS (90% de) <KHMDS (>96% de).

Hydrolysis of the Vinyl Ether and Reagent Recovery (Step 3). The resulting vinyl ether can be hydrolyzed with 10% HCl in acetone at room temperature. The chiral auxiliary is recovered without loss of optical purity and is reusable.

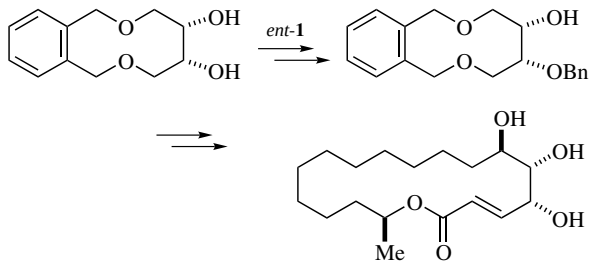
Desymmetrization of Functionalized *meso*-1,2-Diols. Using this methodology, various cyclic *meso*-1,2-diols can be desymmetrized with very high (>96% ee) and predictable selectivity. The enantiomers are obtained through use of an appropriate chiral auxiliary. Bis-sulfoxide **1** has been applied to the desymmetrization of a poly-oxygenated *meso*-diol containing five stereogenic centers (eq 2).



(2)

Allosamizoline

However, the same chiral auxiliary is not suited to the desymmetrization of acyclic *meso*-diols since the acetalization step is sluggish. Nonetheless, an acyclic *meso*-diol such as erythritol can be desymmetrized by prior protection of the terminal primary hydroxyl groups as an *o*-xylyl ether (eq 3).



(3)

Aspicilin

Desymmetrization by means of this methodology was successfully applied to a synthesis of key intermediates for mosin B,[9] aspicilin,[10] *gala*-quercitol,[11] and allosamizoline.[8]

Related Reagents. (1*S*,5*S*)-2*H*-1,5-Benzodithiepin-3(4*H*)-one 1,5-Dioxide.

1. Giolando, D. M.; Kirschbaum, K., *Synthesis* **1992**, 451.
2. Di Furia, F.; Modena, G.; Seraglia, R., *Synthesis* **1984**, 325.
3. Zhao, S. H.; Samuel, O.; Kagan, H. B., *Tetrahedron* **1987**, *43*, 5135.
4. Cohen, Z.; Keinan, E.; Mazur, Y.; Varkony, T. H., *J. Org. Chem.* **1975**, *40*, 2141.
5. Maezaki, N.; Sakamoto, A.; Nagahashi, N.; Soejima, M.; Li, Y. X; Imamura, T.; Kojima, N.; Ohishi, H.; Sakaguchi, K.; Iwata, C.; Tanaka, T., *J. Org. Chem.* **2000**, *65*, 3284.
6. Maezaki, N.; Sakamoto, A.; Soejima, M.; Sakamoto, I.; Li, Y. X.; Tanaka, T.; Ohishi, H.; Sakaguchi, K.; Iwata, C., *Tetrahedron: Asymmetry* **1996**, *7*, 2787.
7. Matsuda, F.; Terashima, S., *Tetrahedron* **1988**, *44*, 4721.
8. Maezaki, N.; Sakamoto, A.; Tanaka, T.; Iwata, C., *Tetrahedron: Asymmetry* **1998**, *9*, 179.
9. Maezaki, N.; Kojima, N.; Sakamoto, A.; Iwata, C.; Tanaka, T., *Org. Lett.* **2001**, *3*, 429.
10. Maezaki, N.; Li, Y. X.; Ohkubo, K.; Goda, S.; Iwata, C.; Tanaka, T., *Tetrahedron* **2000**, *56*, 4405.
11. Maezaki, N.; Nagahashi, N.; Yoshigami, R.; Iwata, C.; Tanaka, T., *Tetrahedron Lett.* **1999**, *40*, 3781.

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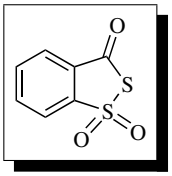
3*H*-1,2-Benzodithiol-3-one 1,1-Dioxide



[66304-01-6] $C_7H_4O_3S_2$ (MW 200.24)
InChI = 1/C7H4O3S2/c8-7-5-3-1-2-4-6(5)12(9,10)11-7/h1-4H
InChIKey = JUDOLRSMWHVKGX-UHFFFAOYAQ

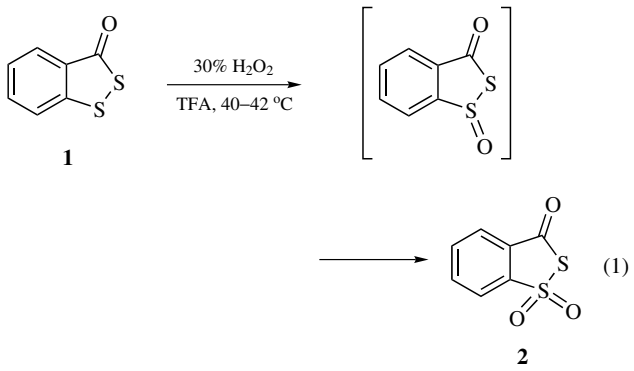
(reagent extensively used in the efficient conversion of phosphite triesters to phosphorothioate triesters in solid-phase oligonucleotide synthesis)

Alternate Name: Beaucage reagent.
Physical Data: mp 102.5–103 °C.
Solubility: soluble in most organic solvents except nonpolar solvent such as alkanes.
Form Supplied in: white solid.
Analysis of Reagent Purity: ^{13}C NMR, ^{1}H NMR, EI-MS.
Preparative Methods: the reagent is prepared from the oxidation of precursor 3*H*-1,2-benzodithiol-3-one with trifluoroperoxyacetic acid.
Purity: recrystallization from methylene chloride-hexanes.
Handling, Storage, and Precautions: the reagent can be stored indefinitely as a crystalline material in amber glass bottles at ambient temperature. The reagent decomposes rapidly when in contact with inorganic and organic bases. The reagent will also decompose in solution when exposed to glass and/or metallic surfaces.
Disposal: the reagent can be safely discarded in a chemical waste container.

Preparation and Handling of 3*H*-1,2-Benzodithiol-3-one 1,1-Dioxide. The sulfur-transfer reagent 3*H*-1,2-benzodithiol-3-one 1,1-dioxide (**2**, eq 1)[1] is widely used in the preparation of oligonucleoside phosphorothioates, which are especially valuable in the development of therapeutic oligonucleotides against various types of cancer and infectious diseases in humans.[2,3]

The scope of this report is not to provide an exhaustive list of all oligonucleoside phosphorothioates that have been prepared using **2**, but to review those critical issues stemming from the preparation and handling of the reagent along with specific applications of 3*H*-1,2-benzodithiol-3-one 1,1-dioxide as a sulfur-transfer reagent.

In regard to the preparation of **2**, oxidation of 3*H*-1,2-benzodithiol-3-one (**1**) to its 1,1-dioxide (eq 1) has initially been performed by treatment with 3-chloroperbenzoic acid.[4] While such an oxidation reaction appears satisfactory for the preparation of **2** on a small scale, the generation of hydrophobic 3-chlorobenzoic acid during the course of the reaction complicates the purification of the desired product on large scale.

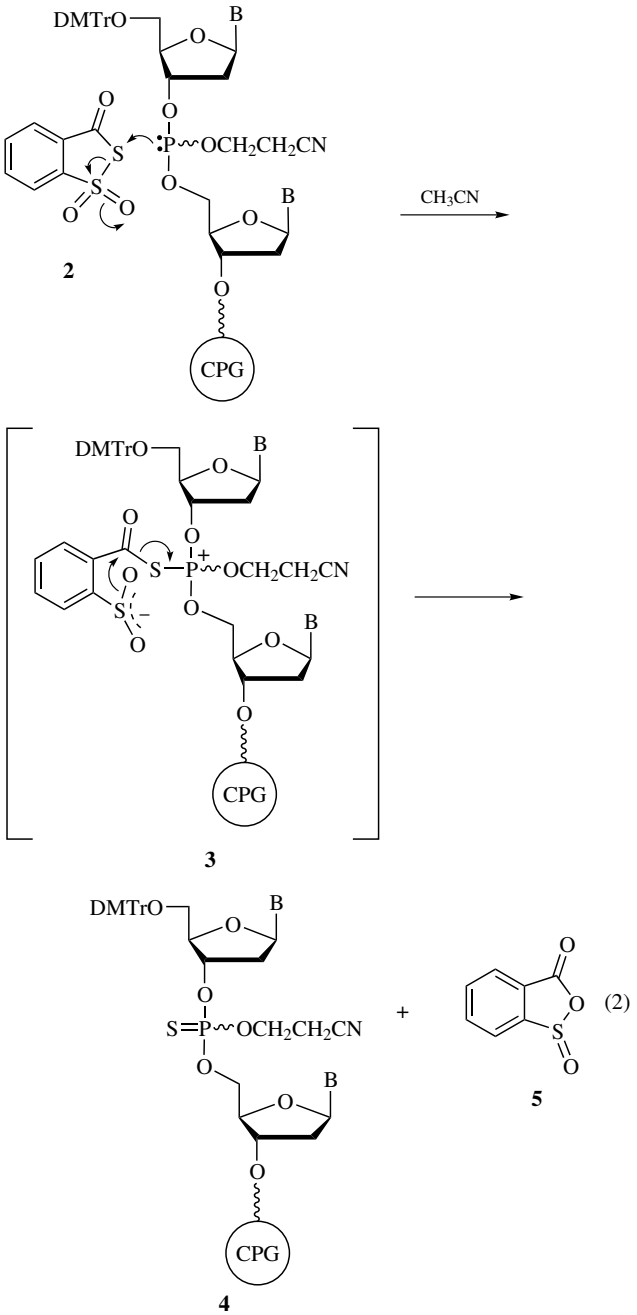


The search for an oxidizing reagent that would produce hydrophilic side-products has identified trifluoroperoxyacetic acid as a promising oxidizer. Oxidation of **1** with trifluoroperoxyacetic acid is efficient only when the internal temperature of the reaction mixture is maintained at 40–42 °C.[1a] As the reaction temperature exceeds 42 °C, the yield of **2** decreases presumably as a result of concurrent hydrolysis of the reagent. At a reaction temperature below 37 °C, the oxidation of **1** becomes sluggish and also results in poorer isolated yields of the 1,1-dioxide (**2**). Thus, when using trifluoroperoxyacetic acid as an oxidizing reagent at 40–42 °C, the preparation of 3*H*-1,2-benzodithiol-3-one 1,1-dioxide can be scaled up to permit facile isolation of the sulfur-transfer reagent in quantities exceeding 125 g, free from peroxide contaminants, upon precipitation on ice.[1c]

In addition to 3-chloroperoxybenzoic acid and trifluoroperoxyacetic acid, dimethyldioxirane is also adequate for the conversion of **1** to its 1,1-dioxide.[5] The reaction of 3*H*-1,2-benzodithiol-3-one with 4 equiv of 70–90 mM dimethyldioxirane in acetone at ambient temperature affords a quantitative yield of the corresponding

1,1-dioxide.[5] While handling dimethyldioxirane on a large scale may be inconvenient, the production of 3*H*-1,2-benzodithiol-3-one 1,1-dioxide in high yields under anhydrous conditions further suggests that hydrolysis is likely responsible for the lower yields of **2** obtained under aqueous conditions.

Sulfurization of tricoordinated phosphorus compounds by treatment with 3*H*-1,2-benzodithiol-3-one 1,1-dioxide results from the nucleophilic attack of, for example, a phosphite triester on the electrophilic thiosulfonate function of **2** to produce the phosphonium sulfinate intermediate **3** (eq 2). Intramolecular condensation of the sulfinate anion with the carbonyl group of the activated thiol ester function releases the phosphorothioate triester (**4**) with concomitant formation of **5**.[1a] Because of the intramolecular nature of the sulfur-transfer reaction, sulfurization of phosphite triesters in oligodeoxyribonucleoside phosphorothioate syntheses is rapid and complete within 30 s at 25 °C. Formation of the intermediate **3** is rate-limiting, as the nucleophilicity of phosphite triesters depends on steric and electronic factors. A striking example of such subtle effects relates to the sulfurization of N^4-benzoyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-*O*-*tert*-butyldimethylsilyl cytidylyl-(3′ → 5′)-N^4-benzoyl-2′-*O*-*tert*-butyldimethylsilylcytidine methylphosphite triester being complete within 30 s upon reaction with **2**,[6] whereas sulfurization of 5′-*O*-(4,4′-dimethoxytrityl)-2′-*O*-methyluridylyl-(3′ → 5′)-N^4-benzoyl-2′-*O*-methylcytidine(2-cyanoethyl) phosphite triester or its 2′-*O*-*tert*-butyldimethylsilyl congener under the same conditions reportedly takes 300 s for completion of the reaction.[7]

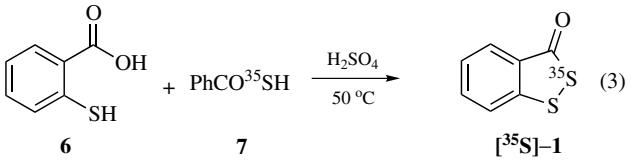


DMTr:4,4′-dimethoxytrityl; B: thymine or any N-protected nucleobase; CPG: controlled pore glass

The production of 3*H*-1,2-benzoxathiolan-3-one 1-oxide (**5**) during the course of the sulfur-transfer reaction effected by **2** appears counterproductive considering that **5** is a potent oxidizing reagent.[1a] It should, however, be noted that the concentration of **5** generated during sulfurization is at least 50-fold lower than that of **2** at all times. Thus, oxidation of phosphite to phosphate triesters caused by **5** during sulfurization is negligible.

Stability of the sulfur-transfer reagent **2** in solution has been questioned by us[1a] and others.[8–12] The reagent decomposes slowly when in contact with glass and/or metallic surfaces. Consequently, any amber glass containers suitable for storing acetonitrile solutions of **2** must first be completely immersed in concentrated sulfuric acid for at least 15 h before being rinsed with distilled water and dried. The container is then filled to ∼20% of its volume with a 10% solution of dichlorodimethylsilane in dichloromethane and vigorously shaken for ∼5 min to ensure uniform distribution of the solution all over its internal surface area. The solution is discarded and the siliconized glass container is thoroughly rinsed with 50% aqueous methanol before being dried in an oven at 110 °C for ∼1 h. Prior to oligonucleotide synthesis, the siliconized glass container is carefully rinsed with acetonitrile to remove any foreign particulates. A 0.05 M solution of **2** in HPLC grade acetonitrile is then filtered through a 45 μm teflon membrane into the siliconized container and stored under a positive pressure of argon on the DNA/RNA synthesizer. Given the incompatibility of **2** with DNA/RNA synthesis reagents, namely, the aqueous iodine solution, the capping solutions, and ammonium hydroxide, it is critically important that the teflon reagent line be carefully cleaned prior to coupling the siliconized container filled with reagent **2** to the instrument. By fulfilling these precautionary measures, acetonitrile solutions of **2** can be used for months on a DNA/RNA synthesizer without noticeable precipitation.

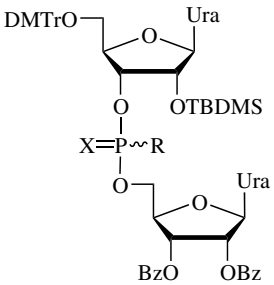
[^{35}S]-3*H*-1,2-Benzodithiol-3-one 1,1-Dioxide in the Synthesis of ^{35}S-labeled Oligonucleoside Phosphorothioates. To facilitate in vivo pharmacokinetic studies of potential therapeutic oligonucleotides such as those DNA, RNA or chimeric RNA–DNA sequences modified with internucleotidic phosphorothioate linkages, mixed phosphodiester-phosphorothioate linkages or mixed phosphorothioate-methyl phosphonate linkages, ^{35}S-labeling of these oligonucleotide analogues is a viable approach. In an attempt to prepare the sulfur-transfer reagent **[^{35}S]-2** for this purpose, the synthesis of **[^{35}S]-1** is accomplished according to eq 3.[13]



6 **7** **[^{35}S]–1**

Typically, thiosalicylic acid (**6**) is heated with ^{35}S-thiobenzoic acid (**7**) and concentrated sulfuric acid at 50 °C to afford [^{35}S]-3*H*-1,2-benzodithiol-3-one in 60% yield. Conversion of **[^{35}S]-1** to its 1,1-dioxide **[^{35}S]-2** is performed according to eq 1. The radiolabeled sulfur-transfer reagent exhibits a specific activity of 91 μCi/μmol and is isolated in ~30% yield from **6**.[13]

Sulfurization of *H*-Phosphonate and *H*-Phosphonothioate Diesters Using 3*H*-1,2-benzodithiol-3-one 1,1-Dioxide. Considering the efficiency with which phosphite triesters are converted to the corresponding phosphorothioate triesters upon reaction with **2**, investigations on the use of 3*H*-1,2-benzodithiol-3-one 1,1-dioxide in the sulfurization of *H*-phosphonate and *H*-phosphonothioate diesters were undertaken.[14] Conversion of the dinucleoside *H*-phosphonothioate diester (**8**) to its dithioated diester (**9**) is accomplished quantitatively within 30 s when a 0.02 M solution of **2** or **1** in 2% aqueous pyridine is used as a sulfurization reagent.



i → **8** X = S, R = H; **9** X = S, R = SH
i → **10** X = O, R = H; **11** X = O, R = SH

(*i*) 0.02M **1** or **2** in 2% aqueous pyridine
Ura, uracil-1-yl; Bz, benzoyl;
TBDMS, *tert*-butyldimethylsilyl

However, conversion of the dinucleoside *H*-phosphonate diester **10** to the phosphorothioate analogue **11** effected by a 0.02 M solution of **2** in 2% aqueous pyridine is relatively slow; it reportedly takes ~3 h for a complete reaction.[14a] While a solution of **2** in 2% aqueous acetonitrile containing triethylamine can completely transform **10** into **11** within 30 s, the use of this sulfurization mixture is incompatible with automated solid-phase oligonucleotide synthesis given the rapid formation of a yellow precipitate caused by triethylamine. In the absence of triethylamine, **10** is not sulfurized under these conditions. Nonetheless, **10** is completely converted to **11** within 20 min when a 0.02 M solution of **1** in 2% aqueous pyridine is used for the sulfurization reaction. Thus, 3*H*-1,2-benzodithiol-3-one in aqueous pyridine is compatible with automated solid-phase synthesis of both DNA and RNA oligonucleoside phosphorodithioates or phosphorothioates from appropriate *H*-phosphonate derivatives.[14a]

3*H*-1,2-Benzodithiol-3-one 1,1-Dioxide and Other Sulfur-Transfer Reagents. Because of its efficiency and rapid sulfurization kinetics, 3*H*-1,2-benzodithiol-3-one 1,1-dioxide has served over the years as a reference standard in the evaluation of a number of sulfurizing reagents for the synthesis of oligonucleoside phosphorothioates.[9,11,15,16] These include phenylacetyl disulfide,[17] tetraethylthiuram disulfide,[18] dibenzoyl tetrasulfide,[19] bis(*O*,*O*-diisopropoxyphosphinothioyl)disulfide,[20] benzyltriethylammonium tetrathiomolybdate,[12] sulfur-triethylamine,[15b] bis(ethoxythiocarbonyl)tetrasulfide,[10] bis(arylsulfonyl)disulfide,[11] pyridinium tetrathionate,[11] bis(isopropylsulfonyl) disulfide,[11] thiiranes,[22] 1,2,4-dithiazoline-3,5-dione,[8,21] 3-ethoxy-1,2,4-dithiazoline-5-one,[8,21] and 3-methyl-1,2,4-dithiazoline-5-one.[16]

Additional Applications of 3*H*-1,2-Benzodithiol-3-one 1,1-Dioxide. In addition to being a potent sulfurizing reagent for phosphite triesters and being particularly useful in the synthesis of phosphorothioated oligonucleotides, 3*H*-1,2-benzodithiol-3-one 1,1-dioxide has also been used in the preparation of phosphorothioated phospholipid derivatives.[23] Also noteworthy is the reaction of 3*H*-1,2-benzodithiol-3-one 1,1-dioxide with excess thiols to generate unstable hydrosulfides, which have been demonstrated to efficiently cause single strand breaks in duplex DNA.[24] Incidentally, the reaction of thiols with **2** is directly analogous to that of phosphite triester with 3*H*-1,2-benzodithiol-3-one 1,1-dioxide.

1. (a) Iyer, R. P.; Phillips, L. R.; Egan, W.; Regan, J. B.; Beaucage, S. L., *J. Org. Chem.* **1990**, *55*, 4693. (b) Iyer, R. P.; Egan, W.; Regan, J. B.; Beaucage, S. L., *J. Am. Chem. Soc.* **1990**, *112*, 1253. (c) Regan, J. B.; Phillips, L. R.; Beaucage S. L., *Org. Prep. Proc. Int.* **1992**, *24*, 488.
2. Crooke, S. T.; Bennett, C. F., *Annu. Rev. Pharmacol. Toxicol.* **1996**, *36*, 107.
3. Beaucage, S. L.; Iyer R. P., *Tetrahedron* **1993**, *49*, 6123.
4. Hortmann, A. G.; Aron, A. J.; Bhattacharya A. K., *J. Org. Chem.* **1978**, *43*, 3374.
5. Marchán, V.; Gibert, M.; Messeguer, A.; Pedroso, E.; Grandas, A., *Synthesis* **1999**, 43.
6. Morvan, F.; Rayner, B.; Imbach, J.-L., *Tetrahedron Lett.* **1990**, *31*, 7149.
7. DiRenzo, A.; Grimm, S.; Levy, K.; Haeberli, P.; Maloney, L.; Usman, N.; Wincott, F., *Nucleosides Nucleotides* **1996**, *15*, 1687.
8. Xu, Q.; Musier-Forsyth, K.; Hammer, R. P.; Barany, G., *Nucleic Acids Res.* **1996**, *24*, 3643.
9. Zhang, Z.; Nichols, A.; Tang, J. X.; Alsbeti, M.; Tang, J. Y., *Nucleosides Nucleotides* **1997**, *16*, 1585.
10. Zhang, Z.; Nichols, A.; Alsbeti, M.; Tang, J. X.; Tang, J. Y., *Tetrahedron Lett.* **1998**, *39*, 2467.
11. Efimov, V. A.; Kalinkina, A. L.; Chakhmakhcheva, O. G.; Hill, T. S.; Jayaraman, K., *Nucleic Acids Res.* **1995**, *23*, 4029.
12. Rao, M. V.; Macfarlane, K., *Tetrahedron Lett.* **1994**, *35*, 6741.
13. Iyer, R. P.; Tan, W.; Yu, D.; Agrawal, S., *Tetrahedron Lett.* **1994**, *35*, 9521.
14. (a) Stawiński, J.; Thelin, M., *J. Org. Chem.* **1991**, *56*, 5169. (b) Stawinski, J.; Thelin, M.; von Stedingk, E., *Nucleosides Nucleotides* **1991**, *10*, 517.
15. (a) Wyrzykiewicz, T. K.; Ravikumar, V. T., *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1519. (b) Cheruvallath, Z. S.; Cole, D. L.; Ravikumar, V. T., *Nucleosides Nucleotides* **1996**, *15*, 1441.
16. Zhang, Z. D.; Nichols, A.; Tang, J. X.; Han, Y. X.; Tang, J. Y., *Tetrahedron Lett.* **1999**, *40*, 2095.
17. Kamer, P. C. J.; Roelen, H. C. P. F.; van den Elst, H.; van der Marel, G. A.; van Boom, J. H., *Tetrahedron Lett.* **1989**, *30*, 6757.
18. Vu, H.; Hirschbein, B. L., *Tetrahedron Lett.* **1991**, *32*, 3005.
19. Rao, M. V.; Reese, C. B.; Zhengyun, Z., *Tetrahedron Lett.* **1992**, *33*, 4839.

20. Stec, W. J.; Uznanski, B.; Wilk, A.; Hirschbein, B. L.; Fearon, K. L.; Bergot, B. J., *Tetrahedron Lett.* **1993**, *34*, 5317.
21. Xu, Q.; Barany, G.; Hammer, R. P.; Musier-Forsyth, K., *Nucleic Acids Res.* **1996**, *24*, 3643.
22. Arterburn, J. B.; Perry M. C., *Tetrahedron Lett.* **1997**, *38*, 7701.
23. Martin, S. F.; Josey, J. A.; Wong, Y.-L.; Dean, D. W., *J. Org. Chem.* **1994**, *59*, 4805.
24. Breydo, L.; Gates, K. S., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 885.

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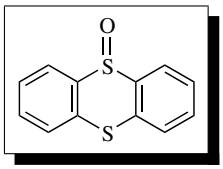
Benzothianthrene Oxide



[2362-50-7] $C_{12}H_8OS_2$ (MW 232.32)
InChI = 1/C12H8OS2/c13-15-11-7-3-1-5-9(11)14-10-6-2-4-8-12(10)15/h1-8H
InChIKey = NYVGTLXTOJKHJN-UHFFFAOYAJ

(reagent used to activate glycals for acylamidoglycosylation and as a probe of the electronic character of oxygen transfer reagents)

Alternate Name: thianthrene monosulfoxide, thianthrene-5-oxide, thianthrene monoxide, Adam probe.

Physical Data: mp 142–144 °C.

Solubility: very soluble in chloroform and acetone, slightly less soluble in glacial acetic acid and benzene, slightly soluble in methanol and ethanol, very slightly soluble in petroleum ether and diethyl ether. Very soluble in boiling water.

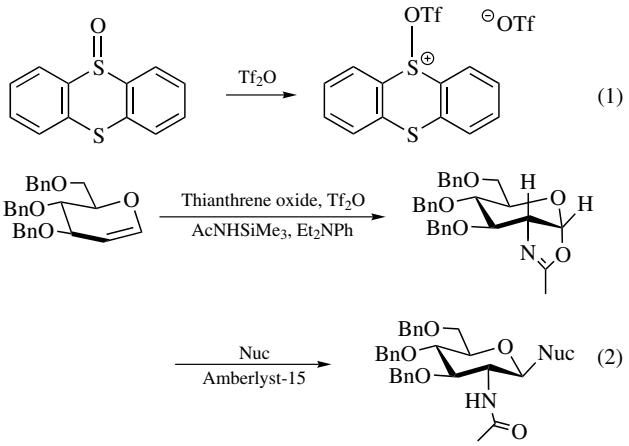
Form Supplied in: off-white crystals.

Preparative Methods: the title reagent has been prepared by the oxidation of thianthrene via numerous methods. The most often cited method is by Gilman and Swayampati,[1] which is actually a modified version of the first reported synthesis by Fries and Vogt.[2] In 86.4 g (0.4 mol) of thianthrene was added 1.4 L of glacial acetic acid and refluxed. To this mixture 150 mL of dilute nitric acid (40%) was added dropwise over 1.5 h. The mixture was further allowed to reflux for 15 min. The yellow solution was diluted with 5 L of ice water and the product was filtered, washed with water, and dried to yield 90.5 g (98%) of off-white crystals of benzothianthrene oxide. Another method is the oxidation of the commercially available thianthrene by *m*-chloroperbenzoic acid (*m*-CPBA).[3,4] To a solution of thianthrene (37 mmol) in CH_2Cl_2 at room temperature, a solution of 88% m-CPBA (50 mmol) in CH_2Cl_2 was slowly added. Once all of the thianthrene got dissolved, the mixture was washed with 2 L of aqueous $NaHCO_3$, then with 1 L of H_2O, dried over $MgSO_4$, and finally concentrated under reduced pressure. The sample was then chromatographed on silica gel utilizing cyclohexane/ethyl acetate (9:1) as eluent to give thianthrene oxide in a good yield.

Purity: title compound forms long off-white needles when recrystallized from methanol, ethanol, or benzene.

Preparation of C2-acetamidoglycosides. Numerous natural oligosaccharide structures contain a C2-acetamidoglycosidic linkage. Due to the biological importance of these carbohydrates, their preparation has been the focus of much research. Glycals have been used to introduce the aza functionality at C2 as an oxime, azide, or sulfonamide. The most notable aspect of these approaches is that they require additional functional group manipulation after introduction of the nitrogen at C2 to form the acetamide group. A direct one-pot preparation of C2-acetamidoglycosides using thianthrene oxide has been reported by Gin.[4] The procedure is one of the most efficient ways to introduce the C2-acetamide linkage in carbohydrates.

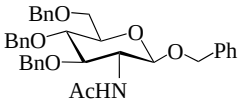
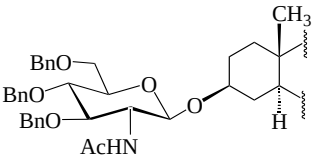
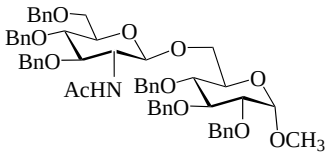
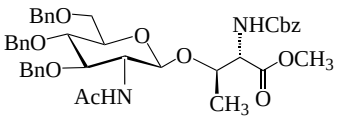
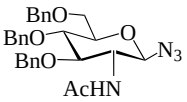
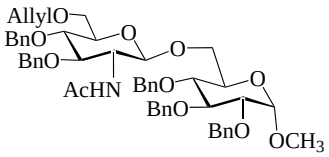
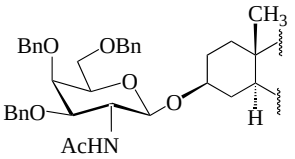
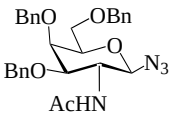
Trifluoromethane sulfonic anhydride and thianthrene oxide form the sulfonium reagent (eq 1) which can activate glycals. Triflic anhydride (2 equiv) is added to a solution of tri-*O*-benzyl glucal (1 equiv) and thianthrene oxide (2 equiv) at −78 °C (eq 2). After activation of the glycal, *N*,*N*′-diethylaniline (4 equiv) and *N*-trimethylsilyl-acetamide (3 equiv) are added and the reaction is stirred at room temperature for 2 h. This sequence converts the glycal to the bicyclic acetimidate intermediate which serves as a glycosyl donor in the subsequent glycosylation step. Introduction of a nucleophile (3 equiv) and Amberlyst-15 acidic resin in the same pot effects glycosylation to form β-C2-acetamidoglycoside in good yields (Table 1). The reaction selectively gave the β-glycosides using both glucal and galactal donors. Activation using thianthrene oxide was found to give enhanced yields relative to other sulfoxide activating agents. The ability of the remote sulfur atom of thianthrene to stabilize the C2-sulfonium and C1-oxocarbenium ions by resonance and direct participation, respectively, was advanced in rationalization of the increased yields.



Attack by nucleophiles such as simple alcohols, cholestarol, carbohydrates, amino acids, and azide was established. The reaction was amenable to various protecting groups on the donor and the acceptor. Camphorsulfonic acid was used in some examples in place of Amberlyst-15 as acidic promoter. Also, with azide as the nucleophile, $Cu(OTf)_2$ was used as the acid promoter. Table 1 collects a number of examples of this procedure showing the glycal and the nucleophile acceptor along with the yield.

The procedure described was extended to the synthesis of other C2-amido glycosides.[4b] Primary amides such as benzamide, 2-benzyloxyacetamide, and pent-4-enamide were used in place of *N*-trimethylacetamide to form the corresponding imidates which

Table 1 Preparation of C2-acetamido glycosides

Glycal	Acceptor	Product	Yield (%)
Tri-*O*-benzyl glucal	Benzyl alcohol		69
Tri-*O*-benzyl glucal	Cholestanol		70
Tri-*O*-benzyl glucal	Methyl 2,3,4-tri-*O*-benzyl glucoside		69
Tri-*O*-benzyl glucal	*N*-Cbz D-threonine methyl ester		65
Tri-*O*-benzyl glucal	Sodium azide		70
6-*O*-allyl-2,3-*O*-benzyl glucal	Methyl 2,3,4-tri-*O*-benzyl glucoside		55
Tri-*O*-benzyl galactal	Cholestanol		51
Tri-*O*-benzyl galactal	Sodium azide		62

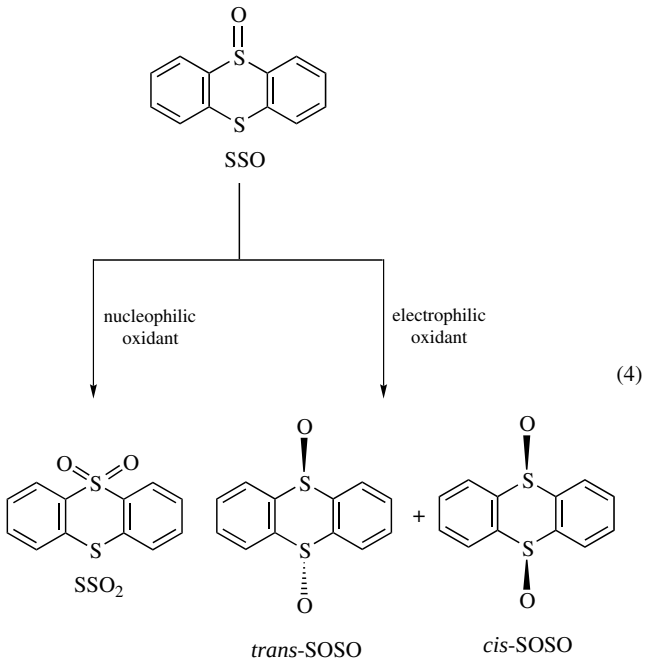
were subsequently glycosylated under the same conditions as the acetimidate. This allowed for the introduction of additional acyl groups at C2 of glucose. The use of trimethylsilyl protected amides was not necessary in the synthesis of these modified glucosamine derivatives as the primary amides themselves were sufficiently reactive as nucleophiles. Seemingly, the trimethylsilyl group in *N*-trimethylsilyl acetamide served only to solubilize this species in the reaction mixture.

Mechanistic Probe in Oxygen Transfer Reactions. It has been extensively demonstrated that benzothianthrene oxide can be chemoselectively oxidized. This has been exploited to determine the electronic character of oxygen transfer agents by quantifying the nucleophilic oxidation at the sulfoxide site of the compound versus total oxidation given by X_{SO} (eq 3).[5] Benzothianthrene oxide is therefore an excellent and widely used probe to determine the nature of various oxidizing agents. The first study employed benzothianthrene oxide (later known as the Adam probe) to distinguish carbonyl oxides from dioxiranes.[6] Subsequently many diverse oxygen transfer systems have been studied using the Adam probe. Some recent examples include dioxygen and peroxides catalyzed by phthalocyanine,[7] peroxy acids,[8] peroxometal complexes,[3] metalloporphyrin catalysts,[9] hemoprotein oxidizing species,[10] heteropolyoxometalate oxidants,[11] persulfoxides,[9] titanium catalysts in heterogenous and homogenous media,[12,13] and surface mediated oxidants.[14]

$$X_{SO} = \frac{\text{nucleophilic oxidation}}{\text{total oxidation}} = \frac{SSO_2 + SOSO_2}{SSO_2 + SOSO + 2SOSO_2} \quad (3)$$

The rationale for the determination of the electronic character of the oxidant is based on the assumption that electrophilic oxidants attack the sulfide group, producing 5,10-dioxides (SOSO), while

nucleophilic oxidants prefer the sulfoxide moiety to yield the sulfone (SSO_2) (eq 4). Over-oxidation of either species gives the sulfone/sulfoxide ($SOSO_2$). Oxidants are then assigned a numerical value, termed the X_{SO} value, to quantify their chemical nature in terms of nucleophilic oxidation. Originally, a value greater than 0.85 constituted a nucleophilic oxidant, while one with a value less than 0.15 was considered electrophilic. Recent work suggested that this basic analysis is slightly more complex than first thought. The later analyses have found that one of the major oxidation products, *trans*-SOSO, was not being seen due to unusually long HPLC retention times. Once this was taken into account, the X_{SO} values for electrophilic oxidants were shifted slightly higher to ≤ 0.3, while the nucleophilic values were shifted slightly lower to ≥ 0.7.[5] The predominant product of electrophilic oxidants is the *trans*-SOSO product. This is explained by noting that the axial lone pair present at the sulfide site is preferentially attacked over the equatorial lone pair.



(4)

Interpretation of the stereo- and chemoselectivity of oxidation reactions using thianthrene oxide must consider its low barrier to ring-inversion, steric effects, and the role that solvents may play in the product distribution.[5,15] All of these possibilities could influence the X_{SO} value of oxidants. Specifically, mechanistic consideration of electrophilic oxidation of thianthrene oxide in the presence of protic solvents or acid leads to diminished yields of SSO_2. Despite all of these concerns, benzothianthrene oxide is still considered a reliable probe for the electronic character of oxidants.

1. Gilman, H.; Swayampati, D. R., *J. Am. Chem. Soc.* **1955**, *77*, 3387.
2. Fries, K.; Vogt, W., *Liebigs Ann. Chem.* **1911**, *381*, 312.
3. Ballistreri, F. P.; Tomaselli, G. A.; Toscano, R. M.; Conte, V.; Di Furia, F., *J. Am. Chem. Soc.* **1991**, *113*, 6209.
4. (a) Di Bussolo, V.; Liu, J.; Huffman, Jr, L. G.; Gin, D. Y., *Angew. Chem., Int. Ed.* **2000**, *39*, 204. (b) Liu, J.; Gin, D. Y., *J. Am. Chem. Soc.* **2002**, *124*, 9789.
5. Adam, W.; Golsch, D.; Görth, F. C., *Chem. Eur. J.* **1996**, *2*, 255.
6. Adam, W.; Haas, W.; Sieker, G., *J. Am. Chem. Soc.* **1984**, *106*, 5020.
7. Sorokin, A. B.; Mangematin, S.; Pergrale, C., *J. Mol. Catal. A.* **2002**, *182*, 267.
8. Eržen, E.; Koller, J.; Plesničar, B., *J. Org. Chem.* **2001**, *66*, 5155.
9. Akasaka, T.; Haranaka, M.; Ando, W., *J. Am. Chem. Soc.* **1991**, *113*, 9898.
10. Alvarez, J. C.; Ortiz de Montellano, P. R., *Biochemistry* **1992**, *31*, 8315.
11. Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y., *J. Org. Chem.* **1993**, *58*, 6421.
12. Adam, W.; Mitchell, C. M.; Saha-Möller, C. R.; Selvam, T.; Weichold, O., *J. Mol. Catal. A.* **2000**, *154*, 251.
13. Adam, W.; Corma, A.; García, H.; Weichold, O., *J. Catal.* **2000**, *196*, 339.
14. Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R., *J. Am. Chem. Soc.* **2000**, *122*, 4280.
15. Deubel, D. V., *J. Org. Chem.* **2001**, *66*, 2686.

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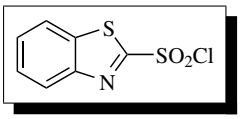
Benzothiazole-2-sulfonyl Chloride



[2824-46-6] $C_7H_4ClNO_2S_2$ (MW 233.7)
InChI = 1/C7H4ClNO2S2/c8-13(10,11)7-9-5-3-1-2-4-6(5)12-7/h1-4H
InChIKey = HSILAFDVJZUQPI-UHFFFAOYAJ

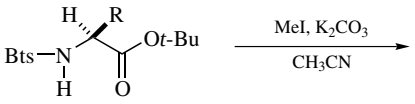
(reagent used as a nitrogen protecting group, in ligand preparation, and in combinatorial sulfonamide libraries)

Physical Data: mp 108–110 °C.[1]
Solubility: soluble in most common organic solvents.
Form Supplied in: not commercially available.
Handling, Storage, and Precaution: this material should not be stored at room temperature for any length of time. The author has had room temperature samples spontaneously decompose with liberation of SO_2. The rate at which this occurs is quality dependent.[2] Dilute solutions in $CHCl_3$ (0.1 M) are relatively stable but a 1 M solution decomposes within 3 days. The stability in solution is improved by the addition of 1% BHT.

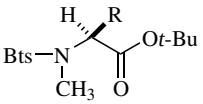
Reagent Preparation. The reagent is easily prepared by a chlorine oxidation of commercially available 2-mercaptobenzothiazole.[2]

Use as a Protecting Group for Nitrogen. Vedejs, who showed that benzothiazole-2-sulfonyl–aminoacids (Bts-aminoacids) could readily be converted to their acid chlorides without racemization, pioneered the use of the Bts group for the protection of amino acids.[3] The acid chloride of Bts-protected amino acids were found to be effective for racemization free peptide couplings.[2] The sulfonamide is readily prepared using

an aq NaOH maintained at pH 10–10.5 by slow addition of 1.3 M NaOH. For simple amines an aq THF mixture of the amine and $NaHCO_3$ is treated with BtsCl to form the sulfonamide. A two-phase system using CH_2Cl_2, H_2O, and $Na_2CO_3$is also effective.[4] Primary Bts derivatives of amines can be alkylated readily (eq 1).[4]



R = Me, *i*-Bu, *i*-Pr



(1)

A number of protocols have been developed for the deprotection of Bts derivatives, and these are listed below. The preferred and probably the mildest methods are those based on the use of a thiol and base.

1. 6 N HCl reflux 2 h.[1]
2. H_3PO_2, DMF, or THF. Best conversions are achieved using lower concentrations (0.05 M, 90%; 0.3 M, 77%; 0.8 M, 43%) for the deprotection of peptides.[3]
3. Zn, AcOH-EtOH.[3]
4. Al(Hg), ether, H_2O.[3]
5. $Na_2S_2O_4$ or $NaHSO_3$, EtOH, and water reflux. With peptides these conditions cause racemization.[3]
6. TFA and PhSH, 25% conversion after 2 days.[3]
7. H_2, Pd/C, and EtOH. Some cleavage occurs before the catalyst is poisoned.[3]
8. NaOH, rt, 12 h can be used for cleavage of secondary amines such as the Bts-proline derivative, but primary derivatives require 90–100 °C for 24 h and result in racemization of the amino acid.[3]
9. $NaBH_4$ and EtOH. This method works for Bts derivatives of 2° amines. With 1° amines the reaction fails to go to completion.[2]
10. PhSH, DIPEA, DMF or PhSH, *t*-BuOK, DMF.[5] K_2CO_3 has also been used as a base.[2] These conditions were effective for both primary and secondary Bts derivatives.
11. Glutathione S-transferase has also been shown to cleave the Bts group.[6] This has considerable significance when using this group as part of a drug candidate.

Other Applications. The Bts group has also been used in the development of ligands[7] and the preparation of sulfonamide libraries for drug development.[8]

1. Roblin, R. O., Jr.; Clapp, J. W., *J. Am. Chem. Soc.* **1950**, *72*, 4890.
2. Vedejs, E.; Kongkittingam, C., *J. Org. Chem.* **2000**, *65*, 2309.
3. Vedejs, E.; Lin, S.; Klapars, A.; Wang, J., *J. Am. Chem. Soc.* **1996**, *118*, 9796.
4. Vedejs, E.; Kongkittingam, C., *J. Org. Chem.* **2001**, *66*, 7355.
5. Wuts, P. G. M.; Gu, R. L.; Northuis, J. M.; Thomas, C. L., *Tetrahedron. Lett.* **1998**, *39*, 9155.
6. Zhao, Z.; Koeplinger, K. A.; Peterson, T.; Conradi, R. A.; Burton, P. S.; Suarato, A.; Heinrikson, R. L.; Tomasselli, A. G., *Drug Met. Disp.* **1999**, *27*, 992.
7. Diltz, S.; Aguirre, G.; Ortega, F.; Walsh, P. J., *Tetrahedron Asym.* **1997**, *8*, 3559.
8. (a) Raghavan, S.; Yang, Z.; Mosley, R. T.; Schleif, W. A.; Gabryelski, L.; Olsen, D. B.; Stahlhut, M.; Kuo, L. C.; Emini, E. A.; Chapman, K. T.; Tat, J. R., *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2855. Hafez, A. A. A.; Geies, A. A.; Hozien, A.; Khalil, Z. H., *Collect. Czech. Chem. Commun.* **1994**, *59*, 957.

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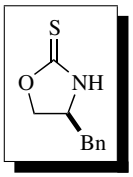
4-Benzyloxazolidine-2-thione

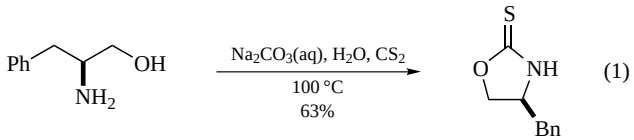


[145588-94-9] $C_{10}H_{11}NOS$ (MW 193.27)
InChI = 1/C10H11NOS/c13-10-11-9(7-12-10)6-8-4-2-1-3-5-8/h1-5,9H,6-7H2,(H,11,13)/f/h11H
InChIKey = WJSUXYCBZFLXIK-WXRBYKJCCW

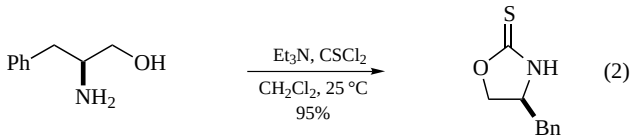
(versatile chiral auxiliary for asymmetric aldol and other asymmetric enolate reactions)

Solubility: soluble in dichloromethane and tetrahydrofuran, low solubility in hexanes.
Form Supplied in: colorless oil.

Methods of Preparation.[1,2] Two methods for the synthesis of 4-benzyloxazolidine-2-thione from 2-amino-3-phenyl-1-propanol (phenylalaninol) have been described. The appropriate amino alcohol is readily prepared from (*R*)-phenylalanine or (*S*)-phenylalanine by reduction with sodium borohydride and iodine in THF.[3] Exposure of phenylalaninol to carbon disulfide and aqueous sodium carbonate for 15 min at 100 °C provided 4-benzyloxazolidine-2-thione in 63% yield (eq 1).[1] Alternatively, the treatment of the amino alcohol with thiophosgene and triethylamine in dichloromethane for 30 min at 25 °C provided 95% of the oxazolidinethione (eq 2).[2] The former method often results in the oxazolidinethione contaminated with varying amounts of the corresponding thiazolidinethione.

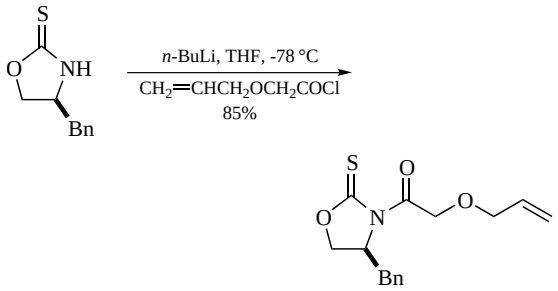


(1)

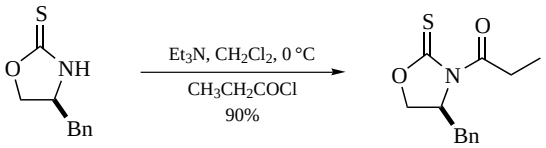


(2)

Methods of *N*-Acylation. Oxazolidinethiones can be *N*-acylated by a variety of standard methods including acylation of the lithium or sodium salts[4] by treatment with an acyl chloride or mixed anhydride (eq 3), or by acylation with an acid chloride in the presence of triethylamine (eq 4).[2,5]

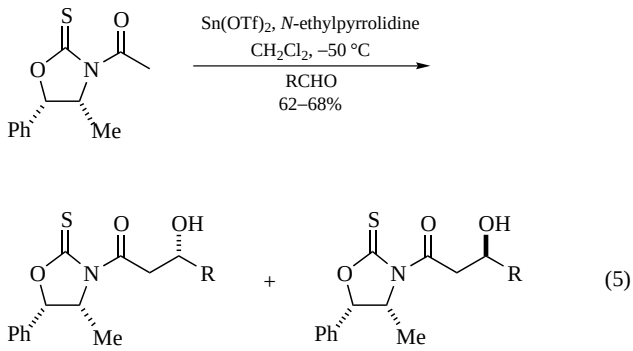


(3)



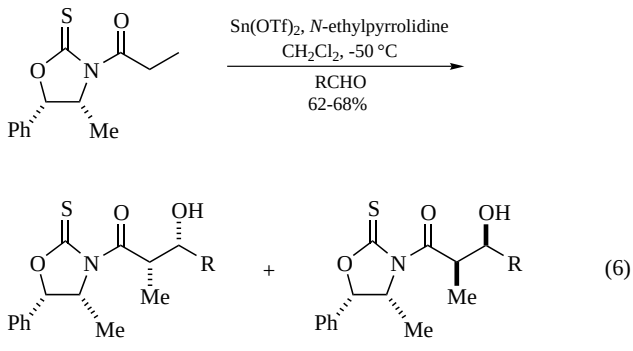
(4)

Tin(II) Enolates of *N*-Acyloxazolidinethiones. Tin(II) enolates of *N*-oxazolidinethiones show moderate diastereoselectivity for the non-Evans aldol products (eqs 5 and 6), presumably proceeding through a chelated transition state.[6] The *N*-acetyl oxazolidinethiones are generally less selective than the corresponding thiazolidinethiones in diastereoselective acetate aldol reactions.



(5)

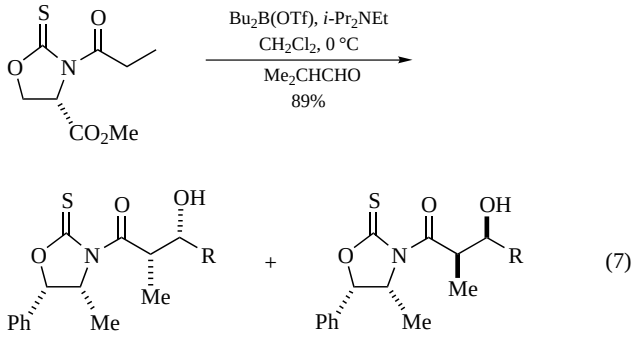
3.2:1 to 8:1



(6)

5:1 to 10:1

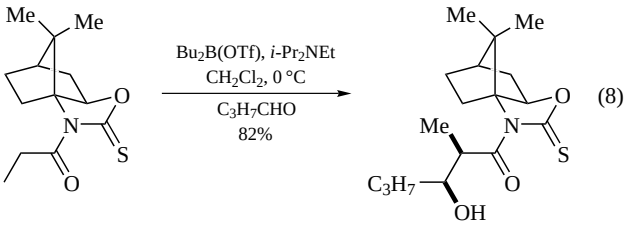
Boron Enolates of *N*-Propionyloxazolidinethiones. Boron enolates of *N*-propionyloxazolidinethiones can be generated under standard enolization conditions with dibutylboron triflate and diisopropylethylamine. The boron enolates react with aldehydes to provide the Evans *syn*-aldol products with excellent diastereoselectivity (eq 7). No oxidative work-up was necessary in the examples reported.[7]



(7)

1:99

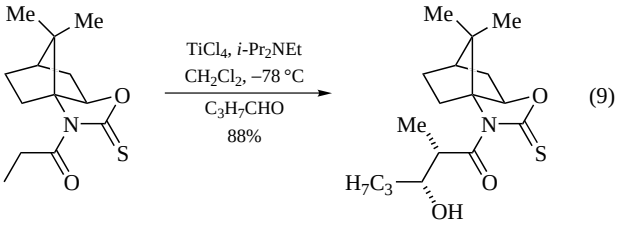
Boron enolates of ketopinnic acid derived oxazolidinethiones have also shown high levels of diastereoselectivity in the aldol addition (eq 8).[4]



(8)

99:1

Titanium(IV) enolates of oxazolidinethiones have been recently popularized as a result of the observation that the titanium(IV) enolates (eq 9), much like the tin (II) enolates, can provide the non-Evans *syn*-aldol adducts.[4]

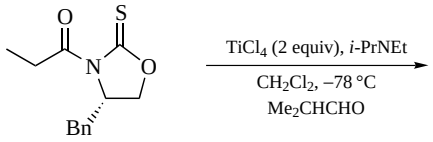


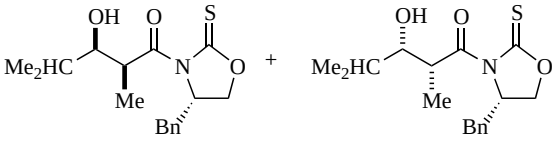
(9)

99:1

Further development of this observation led to the discovery that the readily available titanium(IV) enolate of *N*-propionyl-4-benzyloxazolidine-2-thione can lead to either the non-Evans *syn*- or the Evans *syn*-aldol adducts by virtue of properly controlling the reaction conditions. Exposure of *N*-propionyl-4-benzyloxazolidine-2-thione to 2 equiv of titanium(IV) chloride and diisopropylethylamine followed by the addition of aldehyde produced the non-Evans *syn*-product preferentially (eq 10), while the treatment with 1 equiv of titanium(IV) chloride and 2.2 equiv of (−)-sparteine produced the Evans *syn*-product as the major diastereomer (eq 11).[8] These results led to a proposed model of switching between the chelated and non-chelated transition states.

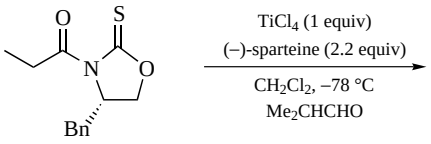
Ultimately, a set of conditions which utilizes 1 equiv of titanium(IV) chloride, 1 equiv of (−)-sparteine, and 1 equiv of *N*-methylpyrrolidinone as a ligand for the metal center was developed to avoid the need for greater than 1 equiv of (−)-sparteine (eq 12).[2] These enolization conditions are also effective for *N*-acyloxazolidinones and *N*-acylthiazolidinethiones.[2]

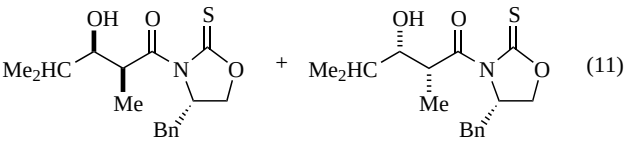




(10)

87% (1:99) + 5% anti

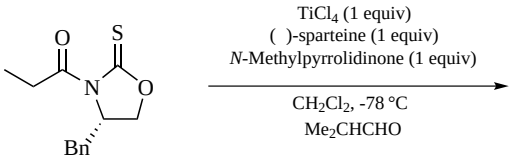


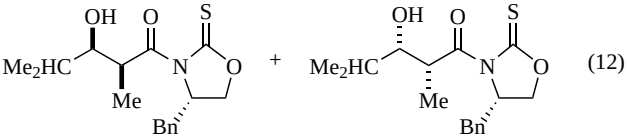


(11)

90% (32:1)

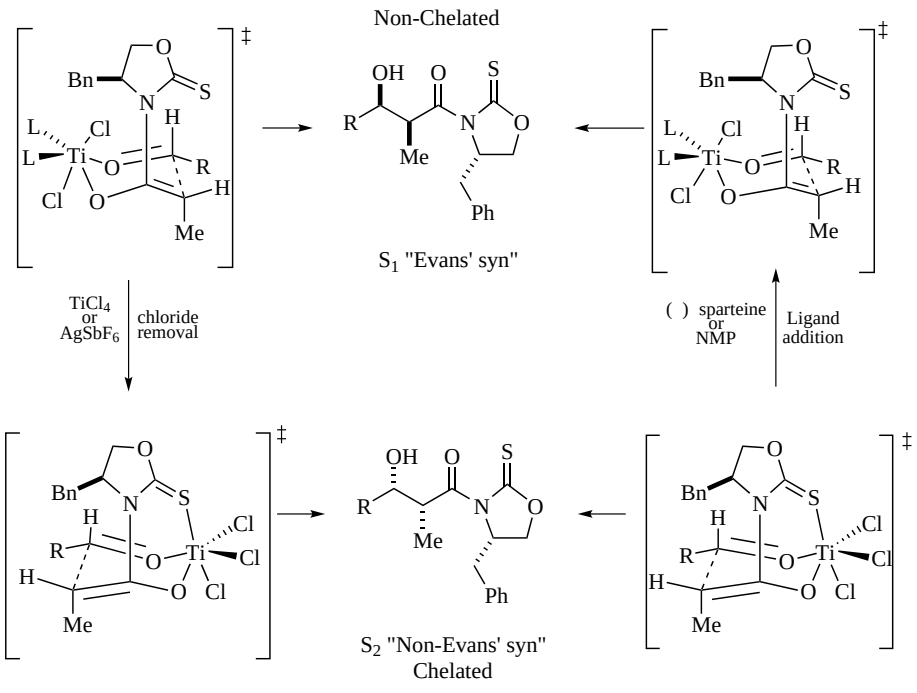
A diastereoselective acetyl variant has been recently developed, which utilizes $TiCl_4$, (−)-sparteine, and NMP enolization conditions with *N*-acetyl-4-isopropyl-5,5-diphenyloxazolidine-2-thione to produce the acetate aldol adducts with very high diastereoselectivity (eq 13).[9]

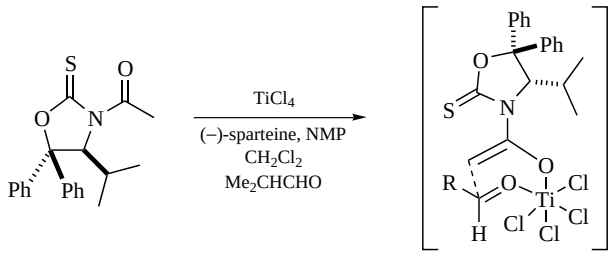


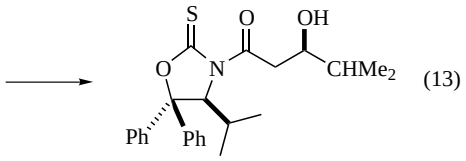


(12)

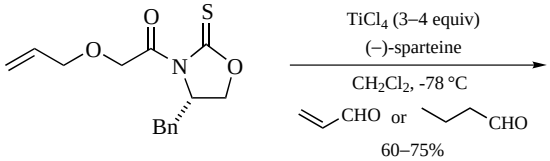
98% (50:1)

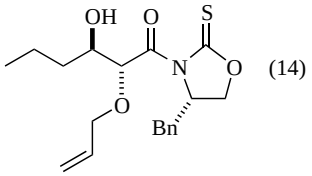




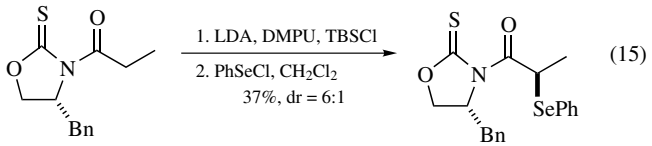


The use of excess titanium(IV) chloride with *N*-glycolyloxazolidinethiones leads to the *anti*-aldol adducts selectively (eq 14). These aldol additions most likely proceed through an open transition state, where the additional Lewis acid serves to activate the aldehyde for the aldol addition reaction.[5]

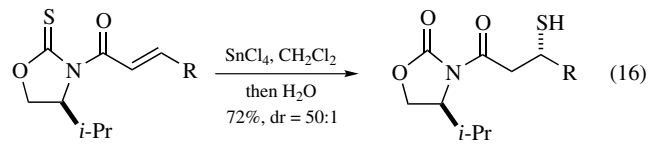




Silyl enol ethers derived from *N*-acyloxazolidinethiones have been treated with phenylselenium chloride to prepare α-selenoimides with good levels of diastereoselection (eq 15), albeit in modest yields.[10]



The tin(IV) chloride enolates of substituted crotonyloxazolidinethiones undergo thermal rearrangement to the 3-mercaptooxazolidinones in yields up to 80% and dr's as high as 50:1 (eq 16).[11]



Related Reagents. 4-Isopropyloxazolidin-2-one; 4-Benzyloxazolidin-2-one; 4-Benzhydryloxazolidin-2-one; 4-Methyl-5-phenyloxazolidin-2-one; 2-Thioxooxazolidine-4-carboxylic Acid methyl Ester; 2-Thioxothiazolidine-4-carboxylic Acid Methyl Ester.

1. Delaunay, D.; Toupet, L.; Le Corre, M., *J. Org. Chem.* **1995**, *60*, 6604.
2. Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K., *J. Org. Chem.* **2001**, *66*, 894.
3. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M., *J. Org. Chem.* **1993**, *58*, 3568.
4. (a) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y., *J. Am. Chem. Soc.* **1993**, *115*, 2613. (b) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S.; Liu, W.-H., *J. Org. Chem.* **1995**, *60*, 3301.
5. Crimmins, M. T.; McDougall, P. J., *Org. Lett.* **2003**, *4*, 591–594.
6. Nagao, Y.; Inone, T.; Hashimoto, K.; Hagiwara, Y.; Ochiai, M.; Fujita, E., *J. Chem. Soc., Chem. Commun.* **1985**, 1418.
7. (a) Hsiao, C.; Miller, M., *Tetrahedron Lett.* **1985**, *26*, 4855. (b) Hsiao, C.; Miller, M., *J. Org. Chem.* **1987**, *52*, 2201.
8. Crimmins, M. T.; King, B. W.; Tabet, E. A., *J. Am. Chem. Soc.* **1998**, *120*, 9084.
9. Guz, N. R.; Phillips, A. J., *Org. Lett.* **2002**, *4*, 2253.
10. Holmes, A., *Tetrahedron: Asymmetry* **1992**, *3*, 1289.
11. Palomo, C., *J. Am. Chem. Soc.* **2001**, *123*, 5602.

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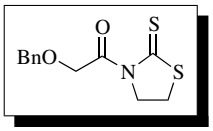
3-(2-Benzyloxyacetyl)thiazolidine-2-thione[1]



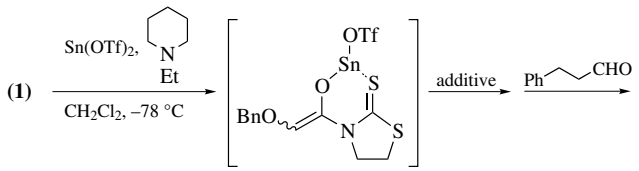
[92486-00-5] $C_{12}H_{13}NO_2S_2$ (MW 267.36)
InChI = 1/C12H13NO2S2/c14-11(13-6-7-17-12(13)16)9-15-8-10-4-2-1-3-5-10/h1-5H,6-9H2
InChIKey = IXLHEGXRGRQHET-UHFFFAOYAF

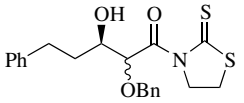
(synthon for α-benzyloxy carboxylic esters, amides, or aldehydes;[2,3] enolate precursor for the diastereo- and enantioselective aldol reactions[4])

Physical Data: mp 81.0–82.0 °C.
Form Supplied in: slightly yellow crystals.
Preparative Methods: methyl 2-hydroxyacetate is converted to methyl 2-benzyloxyacetate (1, NaH; 2, BnBr, DMF, 0 °C to rt, 80%). The acetate is then treated with $LiOH{\cdot}H_2O$ (1.25 equiv) in THF–H_2O at rt to give 2-benzyloxyacetic acid (99%). The acid is converted to the corresponding acid chloride (oxalyl chloride (2.7 equiv, 60 °C, 1.5 h), which is treated with thiazolidine-2-thione in the presence of triethylamine in dichloromethane to give the title reagent **1** (81% from the acid).
Handling, Storage, and Precautions: use in a fume hood.

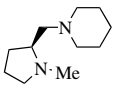
Diastereo- and Enantioselective Aldol Reactions. Optically active 1,2-diol units are widely distributed in natural products such as macrolides, polyethers, and carbohydrates, etc. The aldol reactions of the enolates derived from α-alkoxyacetic acid ester derivatives with aldehydes provide a useful way to construct 1,2-diols,[5] and several asymmetric reactions have been developed.

The tin(II) enolate prepared from (**1**), tin(II) trifluoromethanesulfonate, and 1-ethylpiperidine reacts with aldehydes in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to afford the *anti* aldol adducts in good yields with good selectivities (eq 1). Interestingly, *syn* selective reactions proceed in the absence of TMEDA. Optically active *anti* aldol adducts can be obtained in the presence of chiral diamine (**2**) instead of TMEDA.

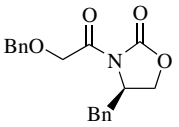




(1)

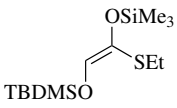
Additive	Yield (%)	*syn*:*anti*	ee (%) *(anti)*
none	62	74:26	–
TMEDA	70	15:85	–
 (**2**)	81	13:87	94

The tin(II) enolate of chiral oxazolidinone derivative (**3**) also works well in the presence of TMEDA to give the *anti* aldol in good yield.[6]

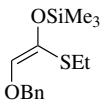


(**3**)

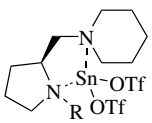
Optically active *syn* and *anti* diol units can be easily prepared by the asymmetric aldol reaction of aldehydes with silyl enolates (**4**) and (**5**), respectively, under the influence of chiral tin(II) Lewis acid (**6**).[7,8] Diastereofacial selectivities are controlled simply by choosing the protective group of the α-alkoxy part of ketene silyl acetals (eqs 2 and 3).



(**4**)

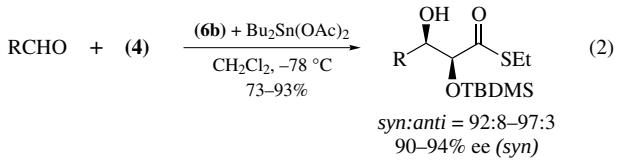


(**5**)

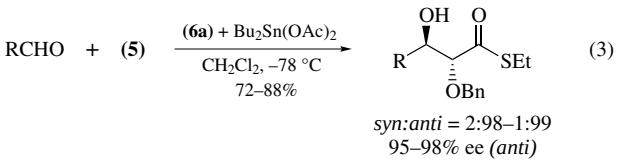


(**6a**) R = Et
(**6b**) R = Pr

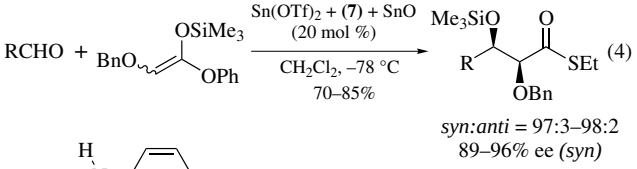
While stoichiometric amounts of chiral sources are required in the reaction of eqs 2 and 3, the truly catalytic asymmetric version is realized by using a novel catalyst system consisting of tin(II) triflate, chiral diamine (**7**), and tin(II) oxide (eq 4).[9]



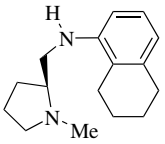
syn:*anti* = 92:8–97:3
90–94% ee *(syn)*



syn:*anti* = 2:98–1:99
95–98% ee *(anti)*



syn:*anti* = 97:3–98:2
89–96% ee *(syn)*



(**7**)

Related Reagents. Ethyl Mandelate; Phenoxyacetic Acid.

1. (a) Mukaiyama, T., *Pure Appl. Chem.* **1983**, *55*, 1749. (b) Mukaiyama, T., *Isr. J. Chem.* **1984**, *24*, 162. (c) Mukaiyama, T., *Chem. Scr.* **1985**, *25*, 13. (d) Mukaiyama, T.; Asami, M., *Top. Curr. Chem.* **1985**, *127*, 133. (e) Mukaiyama, T., *Pure Appl. Chem.* **1986**, *58*, 505.
2. (a) Izawa, T.; Mukaiyama, T., *Chem. Lett.* **1977**, 1443. (b) Izawa, T.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **1979**, *52*, 555.
3. (a) Mukaiyama, T.; Iwasawa, N., *Chem. Lett.* **1982**, 1903. (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T., *Tetrahedron* **1984**, *40*, 1381.
4. Mukaiyama, T.; Iwasawa, N., *Chem. Lett.* **1984**, 753.
5. (a) Touzin, A. M., *Tetrahedron Lett.* **1975**, 1477. (b) Heathcock, C. H.; Hagan, J. P.; Jarvi, E. T.; Pirrung, M. C.; Young, S. D., *J. Am. Chem. Soc.* **1981**, *103*, 4972.
6. Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S., *J. Org. Chem.* **1992**, *57*, 1961.
7. Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S., *Chem. Lett.* **1990**, 1019.
8. Mukaiyama, T.; Shiina, I.; Kobayashi, S., *Chem. Lett.* **1991**, 1901.
9. Kobayashi, S.; Kawasuji, T., *Synlett* **1993**, 911.

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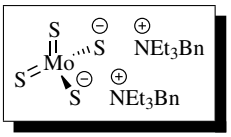
Benzyltriethylammonium Tetrathiomolybdate



[146785-42-4] $C_{26}H_{44}N_2S_4Mo$ (MW 608.85)

InChI = 1/2C13H22N.Mo.4S/c2*1-4-14(5-2,6-3)12-13-10-8-7-9-11-13;;;;;/h2*7-11H,4-6,12H2,1-3H3;;;;;/q2*+1;;;;
2*-1/r2C13H22N.MoS4/c2*1-4-14(5-2,6-3)12-13-10-8-7-9-11-13;2-1(3,4)5/h2*7-11H,4-6,12H2,1-3H3;/q2*+1;-2

InChIKey = BVXREDYYTDDNGI-OWMIBAIBAE

(used as a sulfur transfer reagent and for a variety of reductive transformations)

Physical Data: mp −150 °C (dec.).

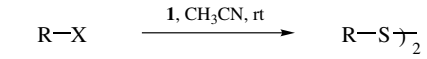
Solubility: soluble in CH_3CN, DMF, and DMSO; sparingly soluble in CH_2Cl_2 and $CHCl_3$.

Form Supplied in: brick red crystals, available as ammonium tetrathiomolybdate.

Preparative Methods: a solution of benzyltriethylammonium chloride (23.3 g, 102.5 mmol) in distilled water (60 ml) was added to a rapidly stirred solution of ammonium tetrathiomolybdate (13 g, 50 mmol) in distilled water (60 ml). Rapid stirring was continued for 2 h at room temperature and the solid that separated was filtered and washed with isopropyl alcohol (40 ml) and ether (40 ml). After drying under high vacuum, red crystals of benzyltriethylammonium tetrathiomolybdate (**1**) (24 g, 80%) were obtained in pure form.

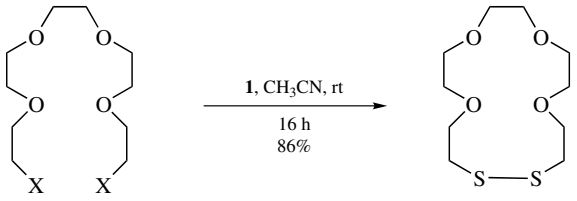
Handling, Storage, and Precaution: stored in nitrogen atmosphere, decomposes on prolonged exposure to air. Incompatible with strong acids and oxidizing agents.

Sulfur Transfer Reactions. Benzyltriethylammonium tetrathiomolybdate (**1**)[1] reacts with aliphatic halides and tosylates at room temperature to provide excellent yields of the corresponding disulfides;[1b] similarly acid chlorides readily react with **1** to produce diacyl disulfides in good yields (eq 1).[1b] The usefulness of this sulfur transfer reaction is exemplified in the synthesis of macrocyclic disulfides and 'redox-switched' crown ethers with ring sizes varying from 7 to 20 in good yields using the corresponding α,ω-dihalides as the precursors without using high dilution techniques (eq 2).[2] Benzyl halides, alkyl iodides, and acyl halides react with **1** by grinding in the solid state at room temperature to afford the corresponding disulfides in good yields.[3] As aliphatic chlorides and bromides do not react with **1** under similar conditions, this methodology is utilized in the selective sulfur transfer reaction on ω-chloro iodides (eq 3).[3] Carbohydrate derived halides (both protected and unprotected) on treatment with **1** form the corresponding disulfides in high yields in a single step (eq 4).[4] Reagent **1** has been used as a sulfur transfer reagent in the successful solid phase synthesis of phosphothioate and macrocyclic diacylglycerol analogs containing disulfides.[5] Activation of various alcohols with DCC and CuCl (catalytic)[6] or HMPT/CCl_4 (catalytic),[7] in a solvent free reaction, followed by treatment with **1** furnishes the corresponding disulfides as the only products in excellent yields (eq 5).[8] A variety of aryl diazonium fluoroborates react with **1** with great facility to yield the corresponding disulfides in moderate to good yields (eq 6).[9]



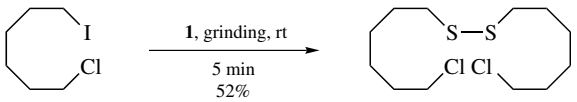
(1)

R = alkyl, acyl
X = halide, tosylate

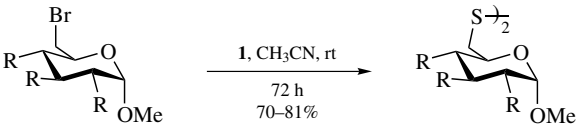


(2)

X = Br, OTs

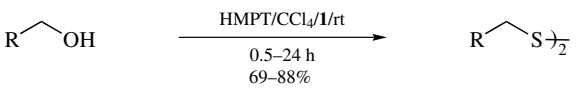


(3)



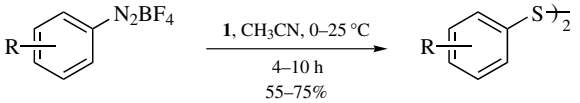
(4)

R = OAc, OH



(5)

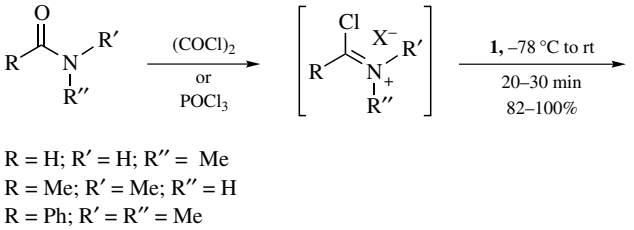
R = phenyl, *p*-Cl-phenyl, propyl, hexyl



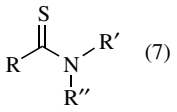
(6)

R = H, Me, OMe, Cl

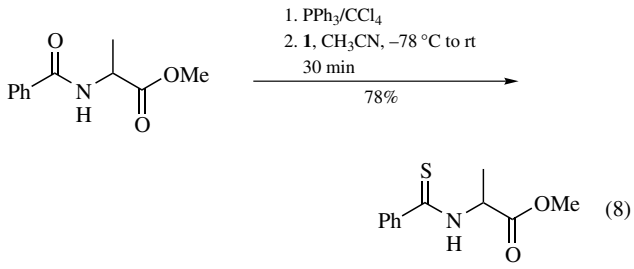
Synthesis of Thioamides/Thiolactams and Thiolactones. Iminium salts, generated in situ from the amides and lactams,[10] react with **1** to produce the corresponding thioamides and thiolactams, respectively, in good yields (eq 7).[11] The advantages of this methodology are the easy work-up and chemoselectively; amides are thionated in the presence of ketones, aldehydes, and esters (eq 8).[1a] ω-Halo acid chlorides react with **1** and the corresponding thiolactones are obtained in moderate yields under mild reaction conditions (eq 9).[12] This reaction works well for the synthesis of small and medium ring thiolactones, but is not useful for the synthesis of macrocyclic thiolactones.[12]



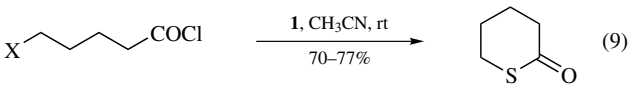
R = H; R′ = H; R″ = Me
R = Me; R′ = Me; R″ = H
R = Ph; R′ = R″ = Me



(7)



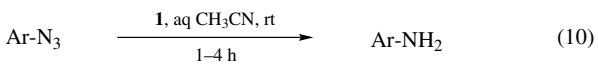
(8)



(9)

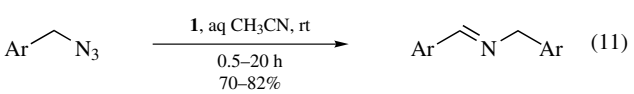
X = I, Br

Reaction of Azides with 1. Aryl azides are reduced by **1** to the corresponding aryl amines at room temperature in very good yields (eq 10).[13] Additionally, the reaction of sulfonyl azides and acyl azides with **1** is very facile at room temperature and produces the corresponding sulfonamides and amides, respectively.[13] However, the same reaction of **1** with aliphatic azides produces the corresponding Schiff base intermediates (eq 11) rather than the amines. α,ω-Diazides on treatment with **1** lead to the corresponding cyclic imines, and this methodology is utilized in the synthesis of an 18-membered macrocyclic system in excellent yields (eq 12).[13] ω-Azido carbonyl compounds undergo smooth reductive cyclization with **1** at room temperature to form the corresponding cyclic imines as the only products.[14] The utilization of this strategy is exemplified in the synthesis of pyrrolobenzodiazepine (PBD) skeleton and in the synthesis of 8-benzyl DC 81 (eq 13).[14]



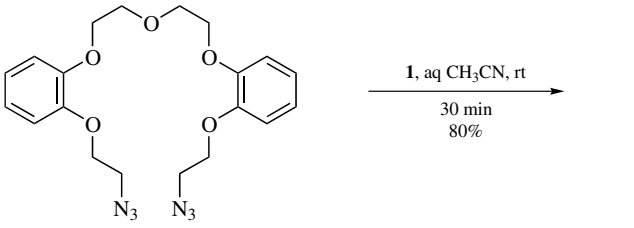
(10)

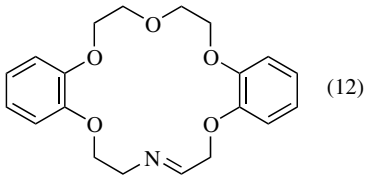
Ar = phenyl, $PhSO_2$, PhCO



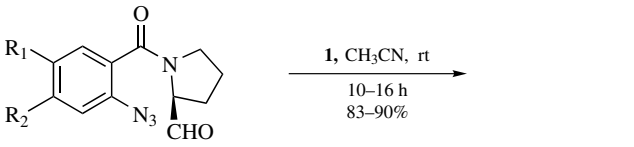
(11)

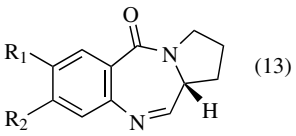
Ar = phenyl, *p*-methoxyphenyl, *p*-nitrophenyl





(12)

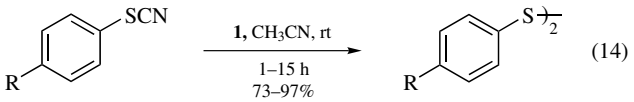




(13)

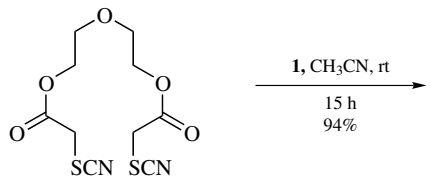
$R_1 = R_2 = H$
DC-81: R_1 = OMe; R_2 = OBn

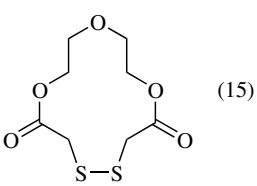
Reductive Dimerization of Organic Thiocyanates and Selenocyanates. Organic thiocyanates undergo reductive dimerization in presence of **1** at room temperature (1 h) to furnish the corresponding disulfides as the only products in good yields (eq 14).[15] This methodology is general and a number of medium and large ring cyclic disulfides are also synthesized from appropriate dithiocyanates (eq 15).[15] This methodology has been exploited in the synthesis of macrocyclic diglycerol disulfides.[16]



(14)

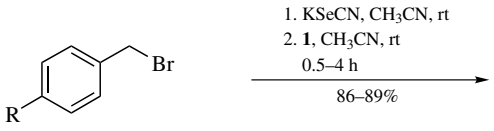
R = H
R = NMe_2



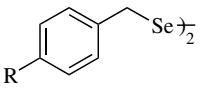


(15)

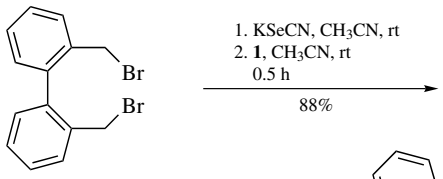
A number of organic selenocyanates, generated in situ by treatment of organic halides with potassium selenocyanate, on treatment with **1** afford the corresponding diselenides in excellent yields in a one-pot operation (eq 16).[17] This methodology is also useful in preparing cyclic diselenides (eq 17), and a number of functional groups such as nitro, ester, cyano, keto, and aldehyde are stable under these reaction conditions.[17]



R = H, NO_2, CN, CO_2Et, COPh

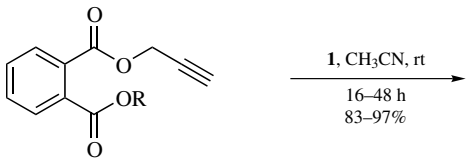


(16)

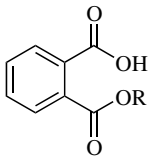


(17)

Selective Deprotection of Propargyl Esters, Ethers, and Carbamates Using 1. Various propargyl esters on reaction with **1** at room temperature provide the corresponding carboxylic acids. This reaction provides an efficient strategy for selective deprotection of propargyl esters in the presence of allyl, benzyl, and *tert*-butyl esters (eq 18).[18] Amino acid derived propargyl esters undergo deprotection with **1** without racemization.

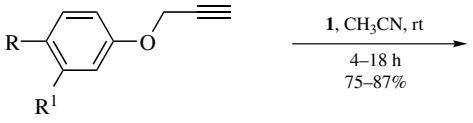


R = allyl, benzyl, *t*-butyl

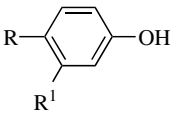


(18)

Protection and deprotection of alcohols is of special interest to organic chemists,[19] particularly in carbohydrate chemistry.[20] Benzyl propargyl ether on treatment with **1** at room temperature in CH_3CN produces the corresponding alcohol in excellent yield. This methodology is general and also useful in the deprotection of propargyl aryl ethers (eq 19).[21] Most of the reducible functional groups in the substrate remain intact under these reaction conditions.

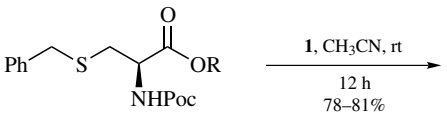


R = $COCH_2CH_3$, R^1= H;
R = CHO, R^1 = OMe
R= *O*-allyl, R^1 = H;
R = *t*-butyl, R^1 = H

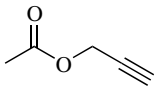


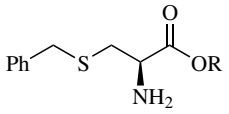
(19)

Propargyloxycarbonyl (Poc) protected amines react with **1** at room temperature and the corresponding amines are obtained in quantitative yields. Deprotection of Poc in *N*-Poc-*S*-benzylcysteine *tert*-butyl ester by **1** has resulted in a selective deprotection of Poc in the presence of methyl, allyl, and *tert*-butyl esters (eq 20).[22] Reaction of **1** with *N*-Poc-*S*-benzylcysteine *tert*-butyl ester is very facile under sonochemical conditions and provides the dipeptide [H_2N-(Bzl)Cys-Cys(Bzl)-O*t*Bu] in 1 h at room temperature.[22] Other protecting groups such as *S*-benzyl and *tert*-butyl groups are unaffected under these reaction conditions. Poc group is stable to acids and bases and deprotection of *tert*-butyl and methyl esters is accomplished conveniently in the presence of *N*-Poc protected amino acid derivatives.



R = Me, *t*-butyl, allyl

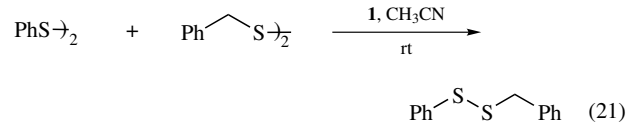
Poc = 

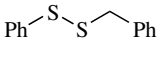


(20)

Multistep Reactions in One-pot Mediated by 1. Reagent **1** can mediate not only the formation of the disulfide bond but can also cleave the disulfide bond under appropriate reaction conditions. A mixture of dibenzyl disulfide and diphenyl disulfide (1:1) in CH_3CN reacts with **1** (2 equiv) at room temperature to provide unsymmetrical disulfide, benzyl phenyl disulfide, as the major product along with the symmetrical disulfides in the ratio of 2:1:1 (eq 21).[23] Diphenyl disulfide on reaction with **1** in the presence of a number of Michael acceptors furnishes the corresponding Michael adducts in very good yields (eq 22). Benzyl bromide reacts with **1** (2 equiv) and methyl vinyl ketone to furnish the corresponding ketosulfide in 86% yield. This multistep reaction (sulfur transfer–reduction–Michael addition) in one-pot is extended to the synthesis of a sulfur-containing bicyclo[3.3.1]nonane skeleton (eq 23).[23] Reagent **1** also reacts with epoxides to form the corresponding dihydroxy disulfides (eq 24). Reaction of disulfides or diselenides with **1** in the presence of epoxides produces the corresponding β-hydroxy sulfides or β-hydroxy selenides,

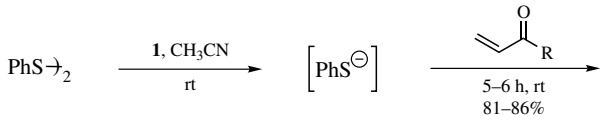
respectively, in good yields (eq 25).[24] An intramolecular version of this tandem reaction is presented in eq 26.

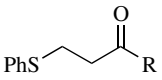




(21)

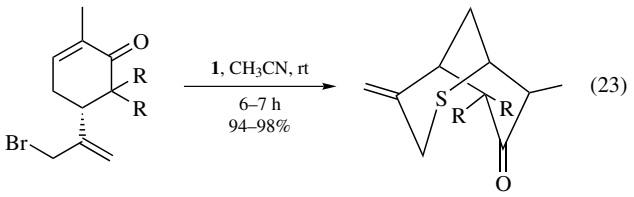
major





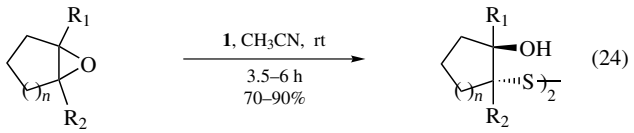
(22)

R = CH_3, OCH_3



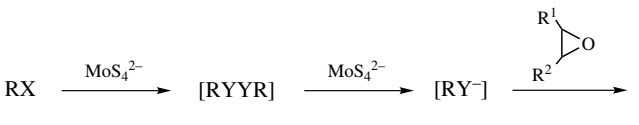
(23)

R = H
R = Me

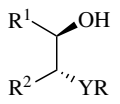


(24)

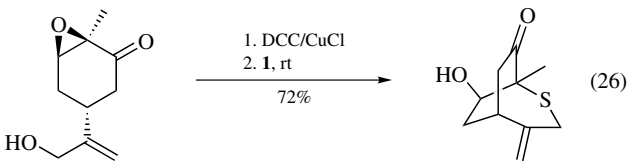
n = 1,2
R_1 = H or CH_3; R_2 = H



X = Br, OTs, SCN, SeCN;
Y = S, Se

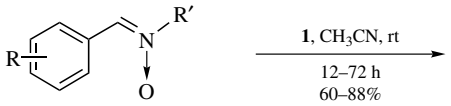


(25)

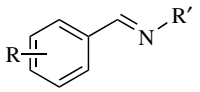


(26)

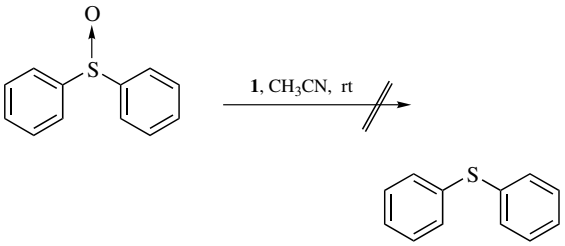
Deoxygenation of Nitrones and *N*-Oxides. Deoxygenation of nitrones and *N*-oxides is a valuable transformation in organic synthesis.[25] Nitrones and *N*-oxides react with **1** to form the corresponding amines and imines, respectively, in good yields. The reaction tolerates most of the reducible functional groups (eq 27).[25] Sulfoxides and azoxy derivatives are unaffected under these reaction conditions (eq 28). Therefore, this methodology offers a unique chemoselectivity in the reduction of *N*-oxides and nitrones in the presence of sulfoxides.



R = H, *p*-Cl, *p*-MeO-, *p*-NO_2
R′ = Ph, Bn



(27)



(28)

Related Reagents. Triphenyl Phosphine; Piperidinium Tetrathiotungstate; Ammonium Tetrathiomolybdate; Lawesson's Reagent.

1. (a) Prabhu, K. R.; Devan, N.; Chandrasekaran, S., *Synlett* **2002**, 1762. (b) Ramesha, A. R.; Chandrasekaran, S., *Synth. Commun.* **1992**, *22*, 3277. (c) Wolff, T. E.; Berg, J. M.; Hodgson, K. O.; Frankel, R. B.; Holm, R. H., *J. Am. Chem. Soc.* **1979**, *101*, 4140.
2. Ramesha, A. R.; Chandrasekaran, S., *J. Org. Chem.* **1994**, *59*, 1354.
3. Ramesha, A. R.; Chandrasekaran, S., *J. Chem. Soc. Perkin Trans. 1* **1994**, 767.
4. Bhar, D.; Chandrasekaran, S., *Carbohydr. Res.* **1997**, *301*, 221.
5. Ghosh, S.; Easwaran, K. R. K.; Bhattacharya, S., *Tetrahedron Lett.* **1996**, *37*, 5769.
6. Mathias, L. J., *Synthesis* **1979**, 561.
7. Castro, B. R., *Org. React.* **1983**, *29*, 1.
8. Sinha, S.; Ilankumaran, P.; Chandrasekaran, S., *Tetrahedron* **1999**, *55*, 14769.
9. Bhar, D.; Chandrasekaran, S., *Synthesis* **1994**, 785.
10. Smith, D. C.; Lee, S. W.; Fuchs, P. L., *J. Org. Chem.* **1994**, *59*, 348.
11. Ilankumaran, P.; Ramesha, A. R.; Chandrasekaran, S., *Tetrahedron Lett.* **1995**, *36*, 8311.
12. Bhar, D.; Chandrasekaran, S., *Tetrahedron* **1997**, *53*, 11835.
13. Ramesha, A. R.; Bhat, S.; Chandrasekaran, S., *J. Org. Chem.* **1995**, *60*, 7682.
14. Prabhu, K. R.; Sivanand, P. S.; Chandrasekaran, S., *Synlett* **1998**, 47.
15. Prabhu, K. R.; Ramesha, A. R.; Chandrasekaran, S., *J. Org. Chem.* **1995**, *60*, 7142.
16. Bhattacharya, S.; Ghosh, S.; Easwaran, K. R. K., *J. Org. Chem.* **1998**, *63*, 9232.
17. Prabhu, K. R.; Chandrasekaran, S., *Chem. Commun.* **1997**, 1021.

18. Ilankumaran, P.; Manoj, N.; Chandrasekaran, S., *Chem. Commun.* **1996**, 1957.
19. Kunz, H.; Waldmann, H., *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1990, Vol 6, p 631.
20. *Protective Groups in Organic Synthesis*; Greene, T. W.; Wuts, P. G. M., Eds.; 3rd ed.; Wiley: New York, 1999, p 17.
21. Swamy, V. M.; Ilankumaran, P.; Chandrasekaran, S., *Synlett* **1997**, 513.
22. Sinha, S.; Ilankumaran, P.; Chandrasekaran, S., *Tetrahedron Lett.* **1999**, *40*, 771.
23. Prabhu, K. R.; Sivanand, P. S.; Chandrasekaran, S., *Angew. Chem., Int. Ed.* **2000**, *39*, 4316.
24. Devan, N.; Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S., *J. Org. Chem.* **2002**, *67*, 9417.
25. Ilankumaran, P.; Chandrasekaran, S., *Tetrahedron Lett.* **1995**, *36*, 4881.

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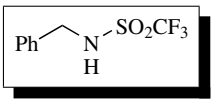
N-Benzyl Triflamide

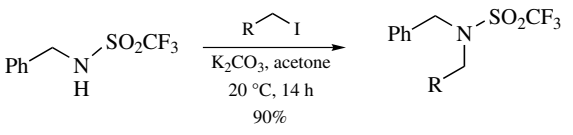


[36457-58-6] $C_8H_8F_3NO_2S$ (MW 239.22)
InChI = 1/C8H8F3NO2S/c9-8(10,11)15(13,14)12-6-7-4-2-1-3-5-7/h1-5,12H,6H2
InChIKey = IJHVVEQTOXFGCL-UHFFFAOYAX

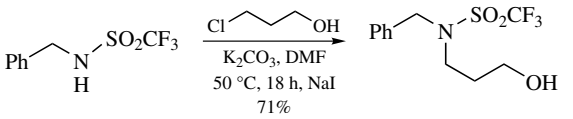
(reagent for the introduction of nitrogen by the Gabriel or Mitsunobu methods)

Alternate Name: N-benzyltrifluoromethanesulfonamide.
Physical Data: colorless solid, mp 44–46 °C.
Solubility: most organic solvents.
Form Supplied in: commercially available as colorless solid.
Purity: crystallization from $CHCl_3$–hexane.[1]
Preparative Methods: [1] triflic anhydride (1 equiv) in dichloromethane is added slowly to a stirred solution of benzylamine (1 equiv) in dichloromethane at 0 °C. After 1 h at 20 °C, the solution is washed with 10% HCl and water then dried (Na_2SO_4) and evaporated to give ca. 90% of *N*-benzyl triflamide as a colorless solid. Crystallization from $CHCl_3$–hexane secures the pure product, δ_H ($CDCl_3$) 7.26 (5H, s), 5.23 (1H,s), and 4.37 (2H, s).
Handling, Storage, and Precaution: the compound is a stable solid; no hazards associated with its handling have been reported. Fluoromethanesulfonamides, in general, are known to possess herbicidal and anti-inflammatory properties.

Gabriel Synthesis of Amines. *N*-Benzyltriflamide was originally introduced as a new nitrogen source for the Gabriel synthesis of amines.[1] Based on its pKa of 6.8 in 67% DMF–water[2] and a gas phase acidity of ΔG_{acid} = 318.8,[3] due to the powerful electron-withdrawing effect of the triflate function, it was reasoned that a weak base should be sufficient to induce the necessary *N*-deprotonation. Typical conditions (eq 1) for *N*-alkylation with primary iodides feature potassium carbonate as the base in acetone at ambient temperature for 14 h.[1] The less reactive 3-chloropropanol required heating in DMF with the same base at 50 °C for 18 h in the presence of sodium iodide to secure a 71% isolated yield of the desired product (eq 2).[4] The derived aldehyde showed useful levels of enantioselection in additions of dialkylzincs catalyzed by (1*R*,2*R*)-bis(trifluoromethanesulfonamido)cyclohexane and titanium isopropoxide.

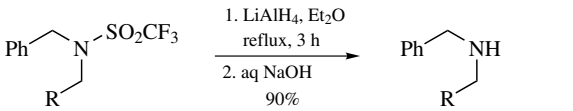


(1)



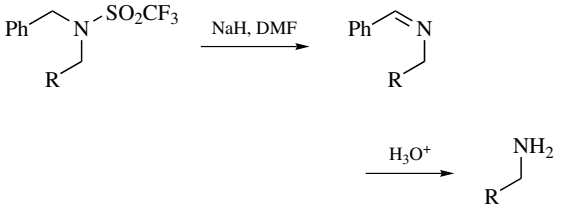
(2)

Deprotection can be achieved in a number of ways, with lithium aluminium hydride seemingly being the reagent of choice to selectively remove the triflate group (eq 3).[1] Yields are excellent, at least with simple substrates. This is in contrast to the removal of triflates from primary amine derivatives, when Red-Al is the preferred reagent, as $LiAlH_4$ forms stable salts with such reactants.



(3)

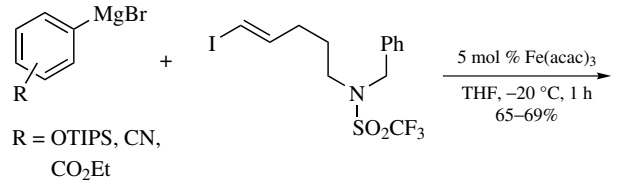
A completely different tactic for the removal of both *N*-protecting groups relies on both the electron-withdrawing properties and the leaving group ability of the triflyl group. Thus, exposure of an *N*-alkyl-*N*-benzyltriflamide to sodium hydride in DMF results in benzylic deprotonation and elimination to give the corresponding imine.[1] Mild acid hydrolysis then gives the free amine (eq 4). Clearly, this has the advantage of benzyl group removal without having to resort to hydrogenolysis, given due attention to the regioselection of the initial deprotonation (i.e., R≠ an electron-withdrawing group).

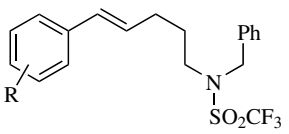


(4)

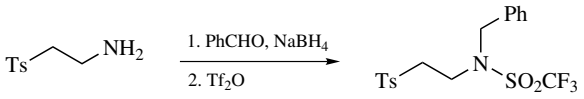
A demonstration of the use of this combination of *N*-protecting groups is shown in a method for coupling aryl Grignard reagents with vinyl iodides (eq 5).[5] Significantly, this iron-catalyzed method features the intermediacy of Grignard reagents having *O*-silyl, cyano, and carboxylate substituents.

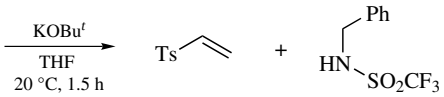
The leaving group ability of a benzyltriflamide group is shown in an example of the use of β-tosylethylamine as a reagent for the protection of secondary amides and carbamates (eq 6).[6] While hardly an alternative preparation of the benzyltriflamide product, this does illustrate well the potential of a β-tosylethyl group as an amine protecting function.





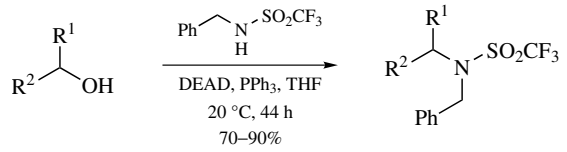
(5)





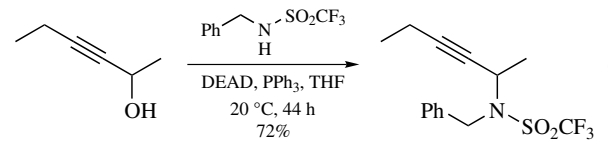
(6)

Mitsunobu Reactions. The rather low pKa of *N*-benzyltriflamide (6.8) suggests that it should be an excellent Mitsunobu nucleophile, in view of the finding that such reagents should have pKa <13.5 to be useful.[7] This turned out to be the case: under standard conditions, good-to-excellent yields of *N*-alkylated benzyltriflamides could be secured from both primary and secondary alcohols (eq 7).[8]



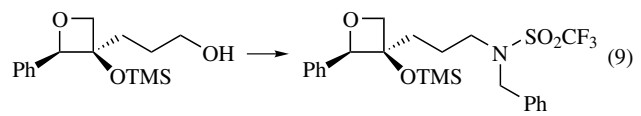
(7)

The two constraints of this reaction are that allylic alcohols tend to give gross mixtures of S_N2 and S_N2' products, and the yields are very poor using cyclohexanols as substrates. The former drawback is partly alleviated by the fact that propargylic alcohols undergo smooth S_N2 displacement under the same conditions (eq 8).[8]



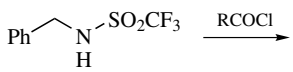
(8)

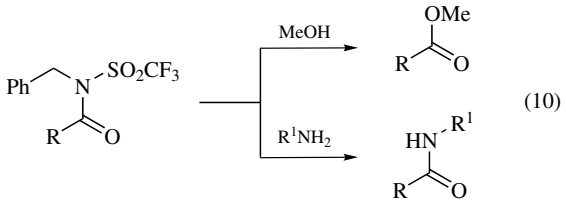
These conditions are sufficiently mild to allow the synthesis of a triflamide from the corresponding oxetane *O*-TMS ether (eq 9),[9] although subsequent attempted removal of the triflate using $LiAlH_4$ destroyed the oxetane.



(9)

Acylating Agents. *N*-Benzyltriflamide reacts smoothly with acid chlorides to give the expected *N*-acyl derivatives.[10] While these are less reactive than acid chlorides, they can act as effective acylating reagents (eq 10).

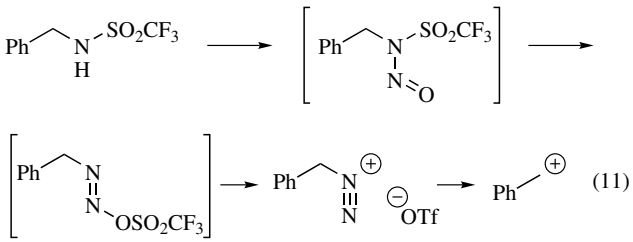




(10)

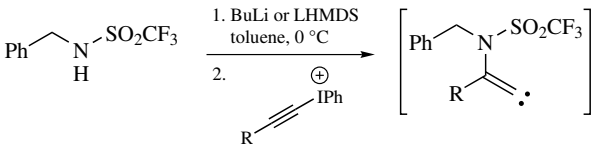
The attack is highly selective in favor of the carbonyl rather than the triflyl function. Further investigations along these lines led to the development of the useful triflating reagent *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$).

Miscellaneous Uses. The high leaving group ability of the triflate group coupled with its inevitably poor nucleophilicity has been exploited in a method for carbenium ion generation by sequential *N*-nitrosation of *N*-benzyl triflamide followed by rapid rearrangement and decomposition (eq 11).[11]

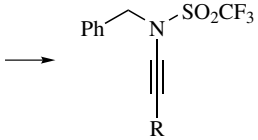


(11)

The electron-withdrawal of the triflyl group also helps stabilize the corresponding ynamine derivatives. These can be prepared by coupling the lithium salt of *N*-benzyltriflamide with an alkynyliodonium triflate in a sequence which probably proceeds via an intermediate vinyl carbene (eq 12).[12] Such products are useful as acetylenic components of intermolecular Pauson–Khand reactions.[13]



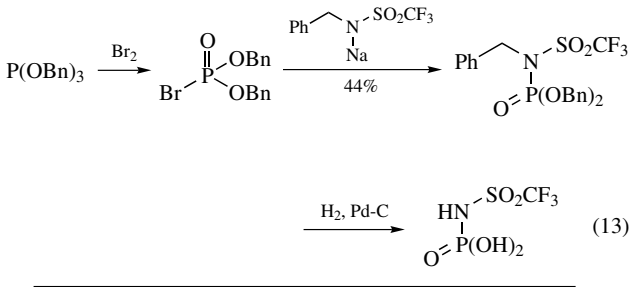
(R = H, TMS)



(12)

The sodium salt of *N*-benzyltriflamide has been found useful in an approach to *N*-sulfonyl-phosphoramidates (eq 13).[14] The neutral conditions during the final deprotection step avoid the P–N bond cleavage associated with a final hydrolysis under acidic conditions. Adducts formed between copper(I) cyanide and

N-benzyltriflamide can be highly effective as catalysts for 1,4-additions to enones.[15]



(13)

1. (a) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D., *Tetrahedron* **1975**, *31*, 2517. (b) Hendrickson, J. B.; Bergeron, R., *Tetrahedron Lett.* **1973**, *14*, 3839.
2. Trepka, R. D.; Harrington, J. K.; Belisle, J. W., *J. Org. Chem.* **1974**, *39*, 1094.
3. Koppel, I. A.; Taft, R.W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignatev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P.-C., *J. Am. Chem. Soc.* **1994**, *116*, 3047.
4. Lutz, C.; Lutz, V.; Knochel, P., *Tetrahedron* **1998**, *54*, 6385.
5. Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P., *Synlett* **2001**, 1901.
6. DiPietro, D.; Borzilleri, R. M.; Weinreb, S. M., *J. Org. Chem.* **1994**, *59*, 5856.
7. Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U., *J. Org. Chem.* **1991**, *56*, 7172.
8. Bell, K. E.; Knight, D. W.; Gravestock, M. B., *Tetrahedron Lett.* **1995**, *36*, 8681.
9. Back, T.; Kather, K.; Krämer, O., *J. Org. Chem.* **1998**, *63*, 1910.
10. Hendrickson, J. B.; Bergeron, R., *Tetrahedron Lett.* **1973**, *14*, 4607.
11. White, E. H.; DePinto, J. T.; Polito, A. J.; Bauer, I.; Roswell, D. F., *J. Am. Chem. Soc.* **1988**, *110*, 3708.
12. Witulski, B.; Stengel, T., *Angew. Chem., Int. Ed.* **1998**, *37*, 489.
13. Witulski, B.; Gößmann M., *Synlett* **2000**, 1793.
14. Burlingham, B. T.; Widlanski, T. S., *J. Org. Chem.* **2001**, *66*, 7561.
15. Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R., *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999.

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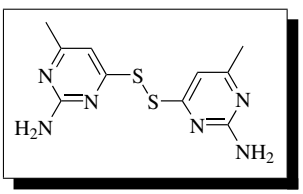
4,4′-Bis(2-amino-6-methylpyrimidyl) Disulfide



[69945-13-7] $C_{10}H_{12}N_6S_2$ (MW 280.37)

InChI = 1/C10H12N6S2/c1-5-3-7(15-9(11)13-5)17-18-8-4-6(2)14-10(12)16-8/h3-4H,1-2H3,(H2,11,13,15)(H2,12,14,16)/f/h11-12H2

InChIKey = CLAPOZGLYFFUHA-LLDOCCBOCU

(in combination with phosphines, induces lactonization of ω-hydroxy acids[1])

Physical Data: mp 207–209 °C.

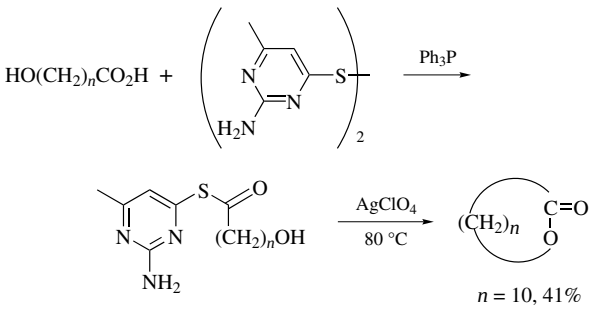
Solubility: sol benzene, acetonitrile.

Form Supplied in: not available from commercial sources.

Preparative Methods: readily prepared from commercially available 2-amino-4-chloro-6-methylpyrimidine, which is treated with $NaS \cdot H_2O$ (5 equiv) in degassed propylene glycol at 140 °C for 3 h. The solution is diluted with H_2O and neutralized with acetic acid. The collected precipitate is recrystallized from ethanol, giving pure 2-amino-4-mercapto-6-methylpyrimidine, which is dimerized with iodine in boiling methanol containing potassium carbonate.

Purification: by crystallization from ethanol or chromatography on silica gel (chloroform–ethanol, 1:1).

4,4′-Bis(2-amino-6-methylpyrimidyl) disulfide and triphenylphosphine form the corresponding thioesters of ω-hydroxy acids, which under high dilution conditions and in the presence of silver(I) perchlorate as a thiol scavenger give the corresponding macrolides (eq 1). Optimal conditions involve 1.5 equiv of both the disulfide and the phosphine, and 1.1 equiv of the silver salt, in refluxing dry benzene for 5 h.[1]



(1)

n = 10, 41%
n = 13, 91%

2,2′-Dipyridyl disulfide and related compounds have also been used as a method for macrolide formation; the addition of thiophilic metal cations and/or pyridine derivatives has been found to assist this process.[2] This oxidation–reduction condensation,[3] using 2,2′-dipyridyl disulfide, constitutes an excellent strategy for the solid-phase synthesis of peptides. This method does not affect amino acids sensitive to oxidation, proceeds under mild conditions without the requirement of basic or acid catalysts, and has the advantages of minimizing both racemization of carboxyl component and side-reactions of certain amino acids.[4] Furthermore, it has been successfully applied to phosphorylation reactions, such as the synthesis of coenzyme A,[5] oligothymidilates, and nucleotide cyclic phosphates,[6] and nucleotides from *O2*,2′-cyclouridine.[7]

1. Nimitz, J. S.; Wollenberg, R. H., *Tetrahedron Lett.* **1978**, 3523.
2. (a) Corey, E. J.; Nicolaou, K. C., *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Gerlach, H.; Thalmann, A., *Helv. Chim. Acta* **1974**, *57*, 2661. (c) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr., *J. Am. Chem. Soc.* **1975**, *97*, 653. (d) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr., *J. Am. Chem. Soc.* **1975**, *97*, 654. (e) Corey, E. J.; Nicolaou, K. C.; Toru, T., *J. Am. Chem. Soc.* **1975**, *97*, 2287. (f) Masamune, S.; Kamata, S.; Schilling, W., *J. Am. Chem. Soc.* **1975**, *97*, 3515. (g) Gerlach, H.; Oertle, K.; Thalmann, A.; Servi, S., *Helv. Chim. Acta* **1975**, *58*, 2036. (h) Gerlach, H.; Thalmann, A., *Helv. Chim. Acta* **1977**, *60*, 2866.
3. Mukaiyama, T.; Matsueda, R.; Suzuki, M., *Tetrahedron Lett.* **1970**, 1901.

4. Mukaiyama, T.; Matsueda, R.; Ueki, M. in *The Peptides*; Gross, E.; Meienhofer, J. Eds.; Academic: New York; 1979, 2, p 383 (*Chem. Abstr.* **1980**, *93*, 150 603h).
5. Hashimoto, M.; Mukaiyama, T., *Chem. Lett.* **1972**, 595.
6. Mukaiyama, T.; Hashimoto, M., *J. Am. Chem. Soc.* **1972**, *94*, 8528.
7. Ogilvie, K. K.; Iwacha, D. J., *Can. J. Chem.* **1974**, *52*, 1787.

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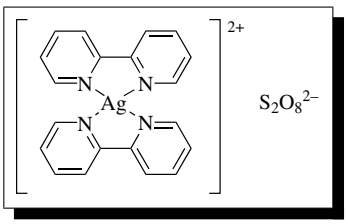
Bis(2,2′-bipyridyl)silver(II) Peroxydisulfate



[47386-36-7] $C_{20}H_{16}AgN_4O_8S_2$ (MW 612.36)
InChI = 1/2C10H8N2.Ag.H2O8S2/c2*1-3-7-11-9(5-1)10-6-2-4-8-12-10;;1-9(2,3)7-8-10(4,5)6/h2*1-8H;;(H,1,2,3)(H,4,5,6)/q;;+2;/p-2/f2C10H8N2.Ag.O8S2/q;;m;-2
InChIKey = DAIVTAFJBBVEGH-BPQXZFCJCW

(one-electron oxidant capable of oxidizing electron-rich aromatic compounds in nucleophilic solvents)

Physical Data: mp 137 °C (dec).

Solubility: slightly sol acetic acid; increased by increasing concentration of acetate ions.

Analysis of Reagent Purity: contents of Ag^{II} can be assayed conveniently by addition of potassium iodide followed by iodometric titration.

Preparative Methods: oxidation of an aqueous suspension of silver nitrate in the presence of 2 equiv of 2,2′-bipyridyl by potassium peroxydisulfate.[1]

Handling, Storage, and Precautions: should be protected from light.

Aromatic Nuclear Substitution. Electron-rich aromatic derivatives react with this reagent in acetic acid containing 0.5 M KOAc to give aryl acetates. Some examples of this stoichiometric reaction are given in Table 1. The reaction closely resembles the electrochemical oxidation of aromatic compounds; isomer distributions are quite similar. Of particular interest is the fact that, in many cases, yields higher than 100% were observed. This was explained by assuming Ag^{II} as the primary oxidant of the aromatic compound followed by reoxidation of the formed Ag^{I} by the counterion peroxydisulfate.[2]

Aromatic Side-chain Substitution. In the case of oxidation of methyl-substituted electron-rich aromatics, benzylic oxidation was observed. For example, 4-methoxytoluene gave, on oxidation in acetic acid/0.5 M KOAc, a mixture of 4-methoxybenzyl acetate and 4-methoxybenzyl alcohol in high yield.[2]

Table 1 Nuclear acetoxylation of arenes using $Ag^{II}(bipy)_2S_2O_8$ in HOAc/0.5 M KOAc

Substrate	Isomer distribution			Yield (%)
	2-OAc	3-OAc	4-OAc	
Anisole	68	0.6	31	63
Biphenyl	21	0	79	18
Naphthalene[a]	95	5		63
4-Bromoanisole	100	0	0	35
4-Fluoroanisole	0	0	100	35
4-*t*-Butylanisole	100	0	0	63

[a]Isomer distribution refers to 1-acetoxy- and 2-acetoxynaphthalene, respectively.

Catalytic Oxidations. As indicated above, the counterion peroxydisulfate can act as a reoxidant for Ag^{I}. This was used in a catalytic version of the above reactions. Thus using a catalytic amount of either the Ag^{II} complex or AgOAc/2,2′-bipyridyl in acetic acid/0.5 M NaOAc and potassium peroxydisulfate as the oxidant, both nuclear and side-chain substitution can be achieved. The addition of barium acetate is important for a high turnover of the catalyst. For some examples, see Table 2.[2]

Table 2 Catalytic acetoxylations of some aromatic compounds

			Catalyst
Substrate	Product	Yield (%)	Turnover
1,4-Dimethoxybenzene	2-Acetoxy-1,4-dimethoxybenzene	33	87
Anisole	Acetoxyanisoles	39	60
4-Bromoanisole	2-Acetoxy-4-bromoanisole	40	56
4-Methoxytoluene	4-Methoxybenzylacetate	35[a]	75

[a]The byproduct 4-methoxybenzaldehyde, formed when using the preformed silver(II) complex as the catalyst, can be avoided by using AgOAc and 2,2′-bipyridyl instead.

---

1. Palmer, W. G. *Experimental Inorganic Chemistry*; Cambridge University Press: Cambridge, 1965.
2. (a) Nyberg, K.; Wistrand, L.-G., *Acta Chem. Scand.* **1976**, *B29*, 629. (b) Nyberg, K.; Wistrand, L.-G., *J. Org. Chem.* **1978**, *43*, 2615.

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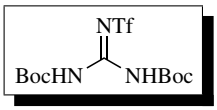
N,N′-Bis(*tert*-butoxycarbonyl)-*N″*-trifluoromethanesulfonylguanidine



[145013-06-5] $C_{12}H_{20}F_3N_3O_6S$ (MW 391.36)

InChI = 1/C12H20F3N3O6S/c1-10(2,3)23-8(19)16-7(17-9(20)24-11(4,5)6)18-25(21,22)12(13,14)15/h1-6H3,(H2,16,17,18,19,20)/f/h16-17H

InChIKey = GOQZIPJCBUYLIR-XQMQJMAZCK

(electrophilic reagent that specifically reacts with amines to yield substituted guanidines[1–4])

Alternate Name: (*tert*-butoxycarbonylamino-trifluoromethanesulfonylimino-methyl)-carbamic acid *tert*-butyl ester.

Physical Data: mp 114–115 °C.

Solubility: soluble in $CHCl_3$, CH_2Cl_2, MeOH, DMF, and most organic solvents; insoluble in H_2O.

Form Supplied in: nonhygroscopic, white crystalline solid.

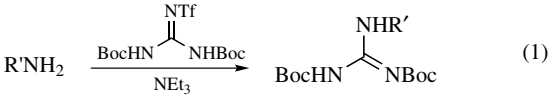
Analysis of Reagent Purity: NMR, HPLC, and elemental analysis.

Preparative Methods: A solution of *N,N′*-diBoc-guanidine (29 mmol) and NEt_3 (36 mmol) in anhydrous CH_2Cl_2 (100 mL) was cooled to −78 °C under N_2. Triflic anhydride (35 mmol) was added dropwise over a period of 20 min, and the resulting mixture was allowed to warm to −20 °C for 4 h. A 2 M aq $NaHSO_4$ solution was added at −20 °C such that the reaction temperature does not rise above −10 °C, and the resulting layers were stirred vigorously for 5 min. The organic layer was washed with 2 M $NaHSO_4$, H_2O, and brine and then dried ($MgSO_4$).[1,2]

Purity: flash column chromatography (20% hexanes in CH_2Cl_2).

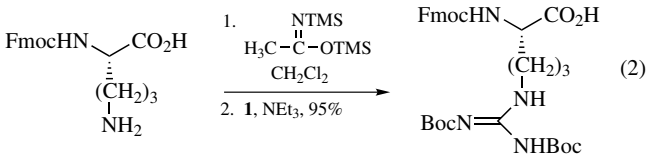
Handling, Storage, and Precaution: indefinitely stable at rt.

Synthesis of Substituted Guanidines. *N,N′*-Bis(tert-butoxycarbonyl)-*N″*-trifluromethanesulfonyl guanidine (**1**) serves as an efficient electrophilic species for the guanidinylation of a variety of amines under mild conditions to give high yields (75–100%) of substituted, protected guanidines (eq 1).[1,2] Its use is limited, however, to the guanidinylation of primary and secondary amines. Aromatic amines react somewhat slower and hindered secondary amines such as diisopropylamine do not react at all. The reaction proceeds most efficiently in nonpolar solvents such as CH_2Cl_2 and $CHCl_3$ although reactions have been successfully carried out in polar solvents such as DMF and MeOH. In a typical reaction, reagent **1** is added as a solid to a slight excess of amine followed by 1 equiv of NEt_3.[3,4] This transformation is not moisture sensitive. After completion of the reaction determined by TLC, the excess starting amines, NEt_3 and triflic amide are removed by aqueous work up. Kinetic studies of several guanidinylating reagents showed compound **1** and *N,N′*-diBoc-thiourea with the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide)[5] gave very rapid product formation.[1] Between these two reagents, the thiourea seems to be superior for sterically hindered amines, but experimental setup and product isolation are much less demanding for reagent **1**. The reaction using *N,N′*-diBoc-1*H*-pyrazole-1-carboxamidine[6,7] proceeded much slower and *N,N′*-diBoc-isothiourea[8] did not react at all. (All reactions were carried out using the recommended solvent.) The *N,N′*-diCbz[1,2] and *N,N′*-diAlloc derivatives of reagent **1** have also been prepared starting from guanidine hydrochloride. These compounds work similar to reagent **1** and their use is advantageous when different protecting groups are required.



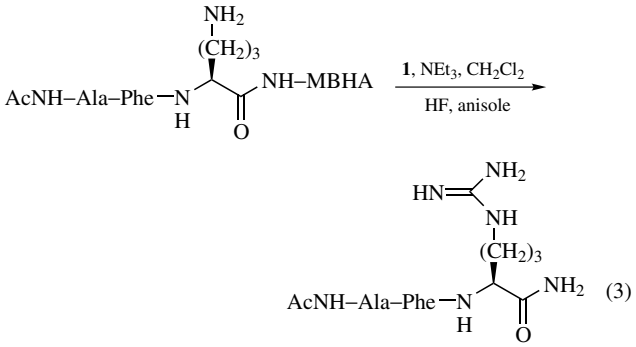
(1)

Modification of Amino Acids and Peptides in Solution. Orthogonally protected amino acids and peptides react in the same manner as described above; however, a different protocol is used for the guanidinylation of *N*-α-ornithine and lysine derivatives that are insoluble in CH_2Cl_2 (eq 2).[1] It is necessary to first convert these compounds into soluble derivatives by silylation with methyl(trimethylsilyl)trifluoroacetamide in refluxing CH_2Cl_2 under N_2. A slight excess of reagent **1** is then added at room temperature followed by NEt_3. Yields of greater than 90% are typical.



(2)

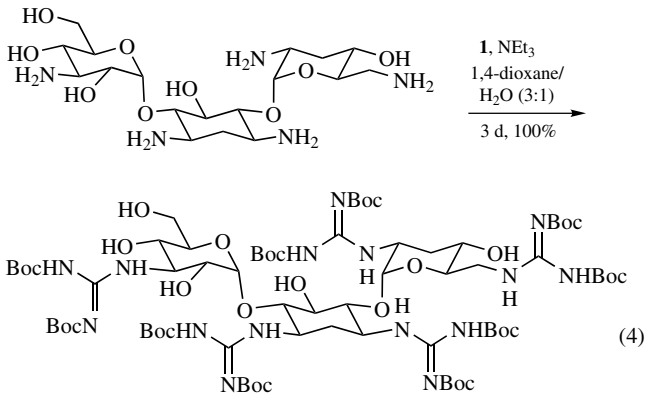
Modification of Peptides on Solid Support. As with 4-nitro-1*H*-pyrazole-*N,N′*-diBoc-1-carboxamidine,[9] reagent **1** can guanidinylate ornithine and lysine residues of a peptide on solid support using a similar protocol as described in the first section (eq 3).[2] Once the desired peptide is constructed on the resin of choice and the amino-protecting group is removed, the free amino function is guanidinylated by treatment with a solution of reagent **1** and NEt_3 overnight. This reaction can be accomplished for a peptide with multiple amine-containing residues and even when the amine-containing amino acid of the peptide is proximal to a sterically demanding resin.



(3)

Preparation of Guanidinoglycosides. Reagent **1** is also used to convert aminoglycosides such as tobramycin to the corresponding guanidinoglycosides (eq 4).[10] This transformation is carried

out in a mixture of 1,4-dioxane and H_2O with a three fold excess of reagent **1** and NEt_3 to each amino group. The reaction is carried out at room temperature and takes approximately 3 d for complete conversion. The reaction can be terminated before complete conversion and the partially guanidinylated derivatives can be isolated using flash column chromatography. Other syntheses employ reagents such as 3,5-dimethylpyrazoylformamidinium nitrate[11] and 1*H*-pyrazole-1-carboxamidine hydrochloride[12,13] at elevated temperatures in DMF, but all show limited success presumably because of limited solubility of the aminoglycosides in DMF.



(4)

Related Reagents. 1*H*-Pyrazole-*N*,*N*′-diBoc-1-carboxamidine [*152120-54-2*]; *N*-[Bis(methylthio)methylene]-*p*-toluenesulfonamide [*2651-15-2*]; 2-Methyl-2-Thiopseudourea Sulfate [*867-44-7*]; *O*-Methylisourea Sulfate [*52328-05-9*]; 1*H*-Pyrazole-1-carboxamidine Hydrochloride [*4023-02-3*].

1. Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M., *J. Org. Chem.* **1998**, *63*, 3804.
2. Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M., *J. Org. Chem.* **1998**, *63*, 8432.
3. Baker, T. J.; Goodman, M., *Synthesis Special Issue*, **1999**, 1423.
4. Baker, T. J.; Tomioka, M.; Goodman, M., *Organic Syntheses* **2001**, *78*, 91.
5. Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. J., *Org. Chem.* **1997**, *62*, 1540.
6. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R., *Tetrahedron Lett.* **1993**, *34*, 3389.
7. Drake, B.; Patek, M.; Lebl, M., *Synthesis* **1994**, 579.
8. Bergeron, R. J.; McManis, J. S., *J. Org. Chem.* **1987**, *52*, 1700.
9. Yong, Y. F.; Kowalski, J. A.; Thoen, J. C.; Lipton, M. A., *Tetrahedron Lett.* **1999**, *40*, 53.
10. Baker, T. J.; Luedtke, N. W.; Tor, Y.; Goodman, M., *J. Org. Chem.* **2000**, *65*, 9054.
11. Wessel, H. P.; Banner, D.; Gubernator, K.; Hilpert, K.; Müller, K.; Tschopp, T., *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 751.
12. Cotner, E. S.; Smith, P. J., *J. Org. Chem.* **1998**, *63*, 1737.
13. Hauser, S. L.; Cotner, E. S.; Smith, P. J., *Tetrahedron Lett.* **1999**, *40*, 2865.

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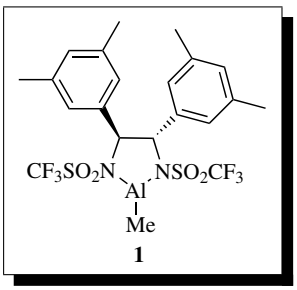
[*N,N′*-[1,2-Bis(3,5-dimethylphenyl)-1,2-ethanediyl]bis(1,1,1-trifluoromethanesulfonamidato)]-methylaluminum[1]



[160207-17-0] $C_{21}H_{23}AlF_6N_2O_4S_2$ (MW 572.51)

InChI = 1/C20H20F6N2O4S2.CH3.Al/c1-11-5-12(2)8-15(7-11)17(27-33(29,30)19(21,22)23)18(28-34(31,32)20(24,25)26)16-9-13(3)6-14(4)10-16;;/h5-10,17-18H,1-4H3;1H3;/q-2;;+2/t17-,18-;;/m0../s1/rC21H23AlF6N2O4S2/c1-12-6-13(2)9-16(8-12)18-19(17-10-14(3)7-15(4)11-17)30(36(33,34)21(26,27)28)22(5)29(18)35(31,32)20(23,24)25/h6-11,18-19H,1-5H3/t18-,19-/m0/s1

InChIKey = MMFOFSUHNHFBDI-DOQBARTABI

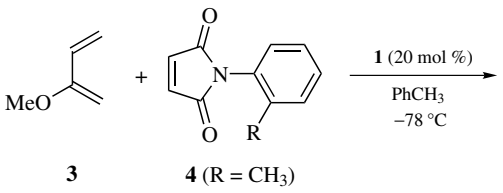
(chiral Lewis acid catalyst for Diels–Alder cycloaddition reactions)

Preparative Methods: prepared immediately before use from the bis(triflamide) of (1*S*,2*S*)- or (1*R*,2*R*)-1,2-(3,5-dimethylphenyl)-1,2-ethylenediamine and trimethyl aluminum.[2–6] Colorless crystals can be obtained from CH_2Cl_2/heptane.

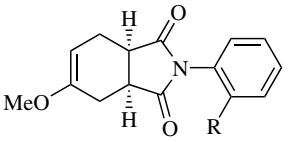
Handling, Storage, and Precautions: the reagent must be prepared using anhydrous conditions under an inert atmosphere. It is important to remove traces of Me_3Al from the reagent by thoroughly drying under vacuum, and/or via crystallization as Me_3Al can also catalyze the Diels–Alder reaction. Methane gas is generated in the preparation of the reagent.

Catalyst for Asymmetric Diels–Alder Reactions. The title reagent (**1**) has been used by Corey and co-workers as a chiral Lewis acid catalyst in asymmetric Diels–Alder cycloaddition reactions.[7] The dimethylphenyl-substituted diazaaluminolidine (**1**) was found to be superior to the related diphenyl-substituted derivative[2] (**2**) in catalyzing the enantioselective reaction of 2-methoxy-1,3-butadiene with *N*-arylmaleimides. Treating a mixture of 2-methoxybutadiene (**3**) and *N*-(*o*-tolyl)maleimide (**4**, R = CH_3) with 20 mol % (*S*,*S*)-(**1**) in toluene at −78 °C affords the corresponding Diels–Alder cycloadduct (**5**) in high chemical yield and in > 90% enantiomeric excess (eq 1).[7] The same reaction performed in the presence of catalyst (**2**) affords (**5**) in significantly diminished 58% ee. The presence of an ortho substituent on the *N*-aryl group of the maleimide dienophile is crucial for high enantioselectivity. Reaction of 2-methoxybutadiene with (**4**) (R = *t*-butyl, I) gives cycloaddition products in uniformly high ee's (> 93%), whereas the same

reaction with (**4**) (R = H) affords (**5**) (R = H) in only 62% ee. Maleic anhydride undergoes cycloaddition with (**3**) in the presence of catalyst (**1**) with no enantioselectivity.



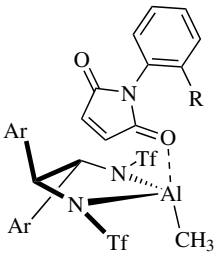
3 **4** (R = CH_3)



(1)

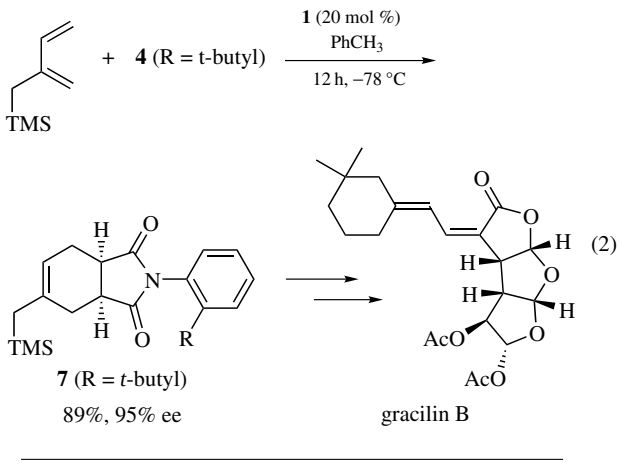
5 (R = CH_3)
98%, 93% ee

Based on the empirical results,[7] X-ray-diffraction data,[8] and solution-phase NMR experiments,[7] a transition state model (**6**) has been advanced to explain the observed enantioselectivity. The presence of an ortho substituent in the *N*-arylmaleimide reactant directs aluminum coordination to occur with the lone pair of electrons anti to the nitrogen atom. A 3,5-dimethylphenyl moiety present on the ethylenediamine framework blocks one face of the dienophile, resulting in approach of the diene from the backside. A considerable amount of spectroscopic evidence, most notably that obtained from NOE (nuclear Overhauser effect) experiments, has been accumulated to support this model.[7] *N*-arylmaleimide derivatives that lack an ortho substituent and other dienophiles (e.g., maleic anhydride) can coordinate to the aluminum catalyst in alternative modes such that the reactive olefin is far removed from the chiral environment of the ligand scaffold, thereby resulting in cycloaddition reactions that exhibit little or no enantioselectivity.



6
Ar = 3,5-dimethylphenyl
Tf = SO_2CF_3

The catalyst (**1**) has been used in the total asymmetric synthesis of marine natural products gracilin B and gracilin C.[9] Treatment of 2-(trimethylsilyl)methylbutadiene with maleimide (**4**) (R = *t*-butyl) in the presence of 20 mol % (*S*,*S*)-(**1**) gave the cycloadduct (**7**) in 95% ee. This material was then converted to the targeted natural products in several steps (eq 2).



(2)

7 (R = *t*-butyl)
89%, 95% ee

gracilin B

Related Reagents. [*N*,*N*′-[1,2-Diphenyl-1,2-ethanediyl]-bis(1,1,1-trifluoromethanesulfonamidato)]methyl Aluminum.

1. Kagan, H. B.; Riant, O., *Chem. Rev.* **1992**, *92*, 1007.
2. Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B., *J. Am. Chem. Soc.* **1989**, *111*, 5493.
3. Corey, E. J.; Lee, D. H.; Sarshar, S., *Tetrahedron: Asymmetry* **1995**, *6*, 3.
4. Corey, E. J.; Kühnle, N. M., *Tetrahedron Lett.* **1997**, *38*, 8631.
5. Pikul, S.; Corey, E. J., *Org. Synth.* **1992**, *71*, 22.
6. Pikul, S.; Corey, E. J., *Org. Synth.* **1992**, *71*, 30.
7. Corey, E. J.; Sarshar, S.; Lee, D. H., *J. Am. Chem. Soc.* **1994**, *116*, 12089.
8. Corey, E. J.; Sarshar, S., *J. Am. Chem. Soc.* **1992**, *114*, 7938.
9. Corey, E. J.; Letavic, M. A., *J. Am. Chem. Soc.* **1995**, *117*, 9616.

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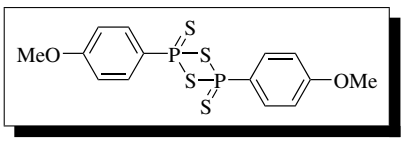
University of Missouri, St. Louis, MO, USA

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide[1]



[19172-47-5] $C_{14}H_{14}O_2P_2S_4$ (MW 404.45)
InChI = 1/C14H14O2P2S4/c1-15-11-3-7-13(8-4-11)17(19)21-18(20,22-17)14-9-5-12(16-2)6-10-14/h3-10H,1-2H3
InChIKey = CFHGBZLNZZVTAY-UHFFFAOYAB

(reagent for the conversion of carbonyl into thiocarbonyl groups[1])

Alternate Name: Lawesson's reagent.
Physical Data: mp 228–229 °C.
Solubility: modestly sol boiling organic solvents such as toluene, chlorobenzene, anisole, dimethoxyethane.
Form Supplied in: yellowish evil-smelling crystals; typical impurity is P_4S_{10}.
Analysis of Reagent Purity: FTIR spectrum.[1c]
Preparative Methods: reaction of P_4S_{10} with anisole in excess refluxing anisole.[2]
Purification: recrystallization from boiling toluene.
Handling, Storage, and Precautions: can be stored for months at rt if moisture is excluded. Prolonged heating in solution causes

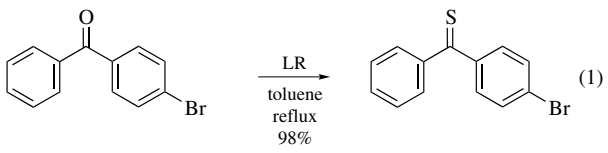
decomposition (polymerization). It is toxic and should be handled under a fume hood since hazardous H_2S is easily liberated with moisture.

Original Commentary

Jürgen Voss
Universität Hamburg, Hamburg, Germany

Thionation of Carbonyl Compounds. Lawesson's reagent (LR) is a most powerful reagent for the thionation of a wide variety of carbonyl compounds. Ketones, enones, carboxylic esters, thiolocarboxylic esters, amides, and related substrates are conveniently transformed into the corresponding thiocarbonyl compounds.[1] In some cases, follow-up products are isolated since certain thiones are labile under the reaction conditions. Compared with P_4S_{10}, from which it is easily prepared,[2] LR exhibits several advantages. Its reactivity is significantly higher and it is sufficiently soluble in hot organic solvents, allowing homogeneous reaction conditions to be applied. Therefore many carbonyl compounds can be successfully thionated with LR but not with P_4S_{10}, or at least thionated in higher yields. Several reagents with structures similar to LR, which are even more reactive or more selective than LR, have been developed and are used in particularly difficult cases. The workup procedure depends on the reaction conditions applied, in particular on the solvent, and the products formed. If DME is used, the reaction mixture can be poured into water and the product extracted as usual. Low boiling hydrocarbons are best evaporated and the residue, which contains the product together with 2,4,6-tris(4-methoxyphenyl)cyclotriphosphoxane 2,4,6-trisulfide, is subjected to column chromatography. High boiling solvents such as tetralin or trichlorobenzene should be removed by flash chromatography in order to avoid thermal decomposition of the labile thiones.

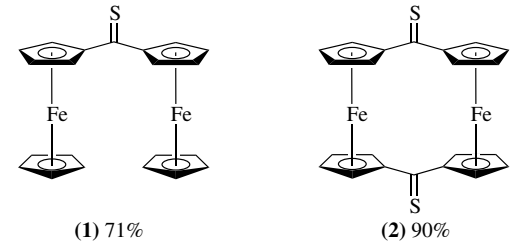
Thioketones. Thioketones of different types have been obtained from the corresponding ketones. Lawesson, who discovered LR to be a powerful reagent for the conversion of C=O into C=S groups, described the preparation of diaryl thioketones.[3] Substituents such as Me, Br, NO_2, or NMe_2 do not affect the good yields of up to 98% (eq 1).



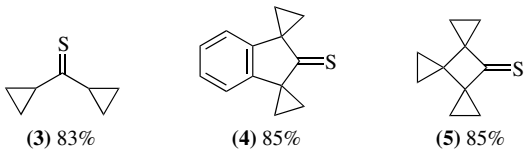
(1)

Recently, the diferrocenyl thioketones (**1**) and (**2**) were prepared from the corresponding ketones.[4] Alkyl aryl and dialkyl thioketones (**3**),[3] (**4**),[5] (**5**)[6] are formed in good yields if enethiolization is unfavored or impossible, whereas mainly enethiols are obtained from cycloalkanones (eq 2).[7]

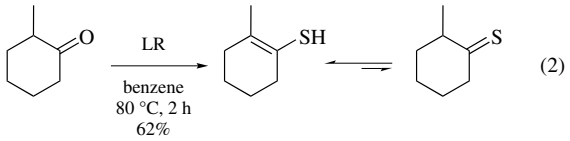
2-Cyclohexenones are thionated with LR (eq 3),[7] but only the vinylogous dithioester (**6**) is a stable compound. Acyclic enones (chalcones) give on reaction with LR the enethione dimers (eq 4).[8]



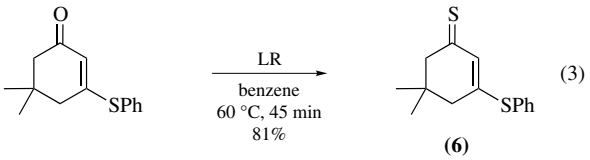
(1) 71% **(2)** 90%



(3) 83% **(4)** 85% **(5)** 85%

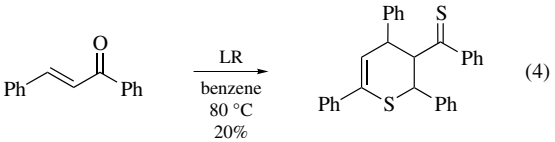


(2)



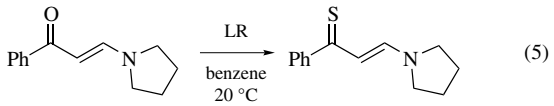
(3)

(6)

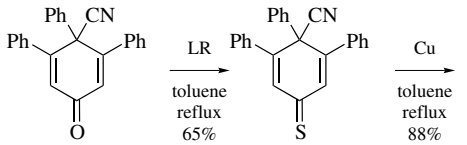


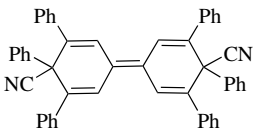
(4)

Again, stable enethiones are formed if an electron donating substituent (e.g. NR_2) is present in the β-position (eq 5).[9] Certain isolable 2,5-cyclohexadienethiones can be further transformed into bicyclohexadienylidenes (eq 6).[10]



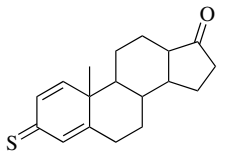
(5)



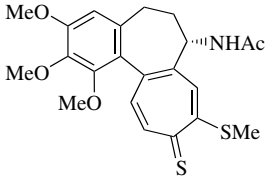


(6)

The thioanalogs of natural products such as the steroid (**7**)[11] or the colchicine alkaloid (**8**)[12] have also been prepared by use of LR.

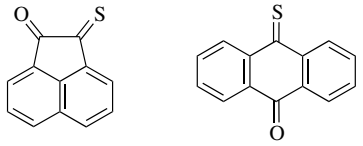


(7) 96%



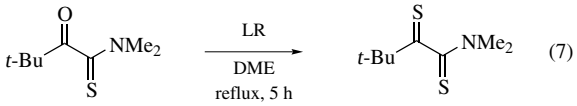
(8) 33%

Thio Analogs of Dicarbonyl Compounds. In general, the most labile thiono analogs of α-dicarbonyl compounds cannot be prepared by any thionation procedure. However, thioacenaphthoquinone (**9**) as well as thioanthraquinone (**10**) were obtained from the quinones and LR.[13] Even α-thioxo thioamides are available (eq 7),[14] whereas 2,2,5,5-tetramethyl-4-thioxo-3-hexanone, which itself cannot be prepared from the corresponding diketone, reacts with LR to yield 3,4-di-*t*-butyl-1,2-dithiete, the valence isomer of the open-chain dithione (eq 8).[15]

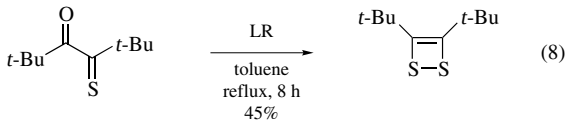


(9) 70%

(10) 65%

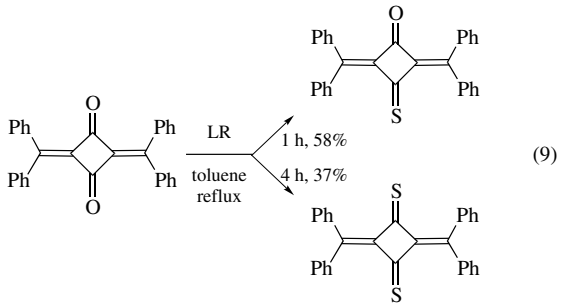


(7)



(8)

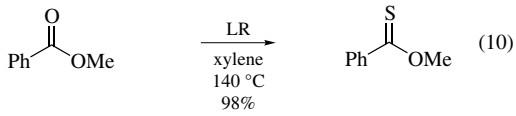
Thioketones with pronounced steric hindrance are obtained on reaction of cyclobutane-1,3-diones with LR (eq 9).[16]



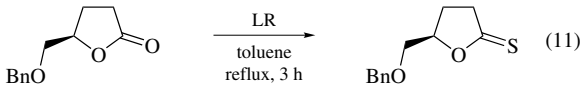
(9)

Diketones with remote C=O groups can be transformed by LR into the mono- or dithiones.[17]

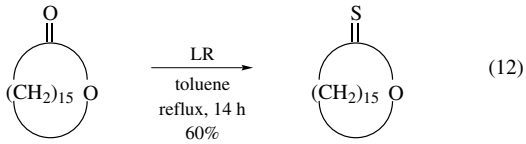
Thiono Esters and Lactones. Although thiono esters can be conveniently prepared via imidates,[18] the introduction of LR for the thionation of esters[3] represents a great advance in synthetic methodology since ordinary esters are used as educts and P_4S_{10} only reacts with esters if enforced reaction conditions are applied, under which many thiono esters decompose. Facile conversion of aliphatic and aromatic esters (eq 10),[3,19] α,β-unsaturated esters,[20] and lactones[21] to the corresponding thiono derivatives is effected in high yields (eqs 11 and 12).[22,23]



(10)

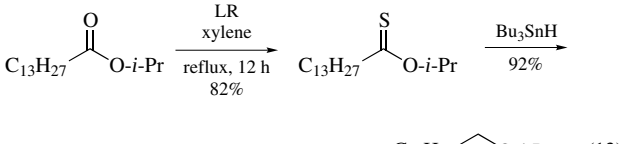


(11)



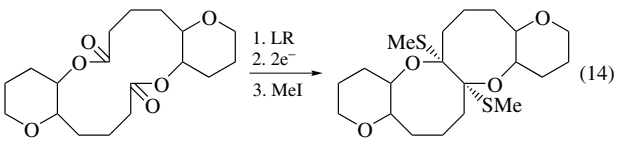
(12)

Thiono esters and lactones are important intermediates in modern organic synthesis since they easily undergo useful follow-up reactions. Ethers are formed on reduction with Raney nickel[24] or tributylstannane (eq 13).[25]

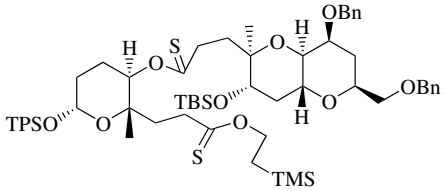


(13)

Macrocyclic bis-thionolactones have been prepared with LR. These were converted by reduction with sodium naphthalenide into the radical anions, which gave bicyclic systems through radical dimerization and subsequent methylation (eq 14).[26] This method was successfully applied by Nicolaou et al.[27] in the total synthesis of hemibrevetoxin B. One of the crucial steps of the synthesis was the preparation of the bis-thiono ester (**11**), which was achieved by using LR together with tetramethylthiourea in xylene at 175 °C.[27]



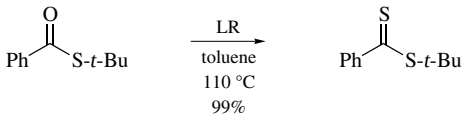
(14)



(11) 49%

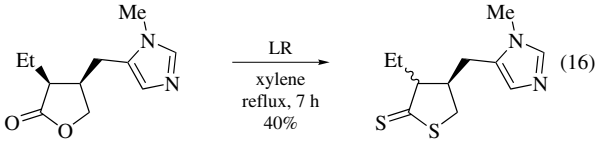
Dithioesters and Related Compounds. Thioesters are transformed into the corresponding dithioesters on reaction with

LR.[3,20,28] Again the yields are nearly quantitative even if steric hindrance can be expected (eq 15).[3]



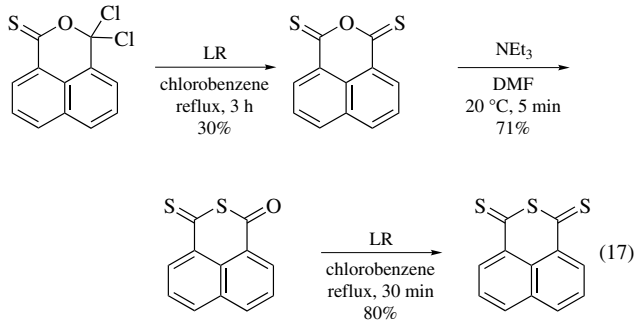
(15)

The reaction is completed within 5–15 min if tetralin at 210 °C is used as solvent.[28] Also, dithio-γ-lactones,[21,28] including dithiophthalides[29] and dithio-α-pyrones,[30] are formed smoothly whereas the hitherto unknown simple β- or δ-dithiolactones cannot be prepared, neither with LR nor by any other method. Interestingly, dithiopilocarpine is formed as a mixture of diastereomers on reaction of pilocarpine with LR (eq 16), i.e. both oxygen atoms of (**12**) are replaced by sulfur.[31] In an interesting sequence of thionation and rearrangement reactions, three different thiono analogs of 1,8-naphthalic anhydride were prepared (eq 17).[32]



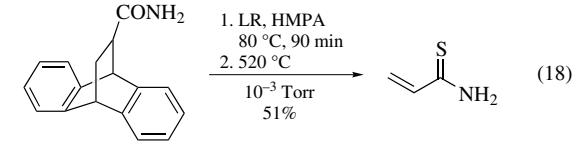
(16)

(**12**)

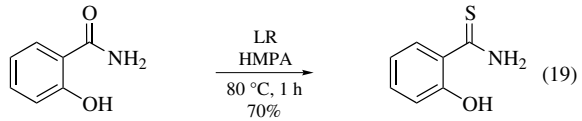


(17)

Thioamides and Related Compounds. Thioamides are the most stable thiocarbonyl compounds and have been prepared, for a century, from amides and P_4S_{10} under rather drastic conditions. However, even for this purpose LR has turned out to be a superior reagent. High yields are obtained for all types of thioamides[1,33] and -lactams[1,33,34] including the elusive unsubstituted acrylothioamide (eq 18)[35] and thioformamides or thioamides bearing sensitive substituents such as NO_2, Z-NH,[36] or OH (eq 19).[33]

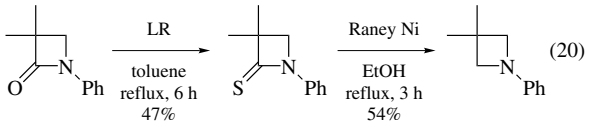


(18)

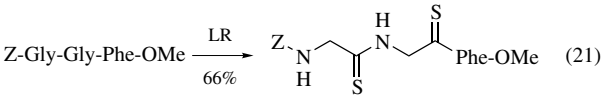


(19)

β-Lactams are also smoothly transformed[34] (eq 20),[37] which is important for the preparation of thio analogs of β-lactam antibiotics or azetidines. Furthermore, endothio oligopeptides became conveniently available only after LR had been introduced as reagent[1,38,39] (eq 21).[40]



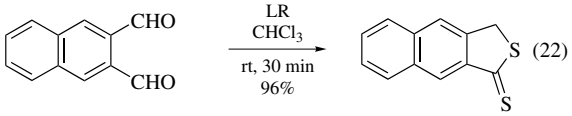
(20)



(21)

Recently the cyclopeptide [D-cysteine]^{8}cyclosporin has been prepared from [D-serine]^{8}cyclosporin via selective thionation with LR at the 7-position followed by intramolecular sulfur transfer.[41]

Miscellaneous Reactions of LR. Under particular conditions, certain carbonyl compounds and other substrates react with LR to form thiophosphonates or heterocycles, which fact throws some light on the mechanism of thionation reactions with LR.[1] Carbinols undergo nucleophilic substitution with LR to form the corresponding thiols.[42] The redox properties of LR can be utilized to prepare dithiolactones from dialdehydes (eq 22),[43] α-oxo thioamides from nitro ketones (eq 23),[44] or sulfides from sulfoxides.[45]



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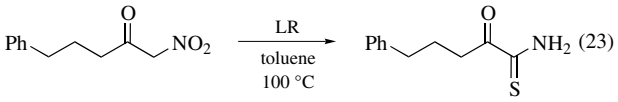
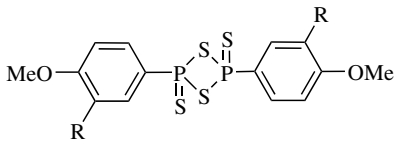


(23)

First Update

Jürgen Voss
Universität Hamburg, Hamburg, Germany

General. Several reviews on 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane disulfide, "Lawesson's Reagent" (LR), have appeared since 1992, which deal with its chemical properties and reactions and, in particular, its use in synthetic chemistry. The most valuable and comprehensive one was authored by Jesberger et al.[46] Li et al. have written a Chinese review article on new applications of LR in organic syntheses.[47] A modification of LR which carries *tert*-butyl substituents (**13**) has been described by Foreman.[48] Compound **13** is better soluble in organic solvents and thus more reactive than LR. Reports on the use of LR in syntheses of thioaldehydes[49] and thioketones[50] have appeared.

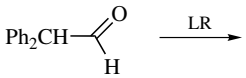


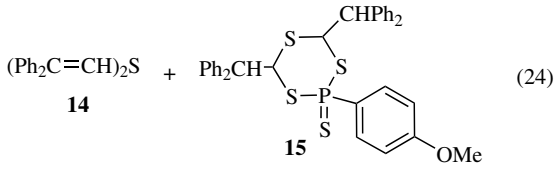
LR: R = H
13: R = *t*-Bu

Some novel findings of general interest concerning the structure of LR[51] and some of its analogs,[52] the NMR spectroscopic properties,[51,53,54] and mechanistic implications of its reactions[52,55] have been reported.

Now as before, the facile transformation of carbonyl compounds into the corresponding thiocarbonyl compounds represents an important application of LR in synthetic organic chemistry. Frequently, however, other useful products such as interesting heterocycles are obtained instead of the expected thiocarbonyl compounds. The frequently formed complex phosphorus- and sulfur-containing heterocycles[56,57] are sometimes undesired as they are less useful for organic syntheses. On the other hand, reactions of LR with other types of starting material have been investigated, which are of interest from an organic chemist's point of view. Reactions which are predominantly inorganic in nature, such as the formation of metal complexes are not considered.

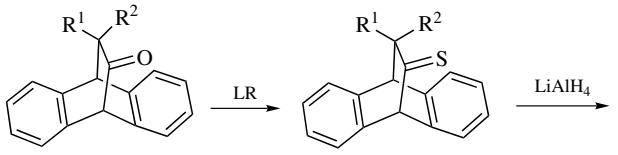
Thionation of Aldehydes. Thioaldehydes are extremely labile compounds. One cannot, therefore, expect that LR will smoothly transform aldehydes into the corresponding thioanalogs.[49] If, for instance, diphenylacetaldehyde reacts with LR the divinylsulfide (**14**) and the 1,3,5-trithia-2-phosphacyclohexane (**15**) are formed instead of the thioaldehyde (eq 24). However, the corresponding enethiols,[58] although terminal (aldo-) enethiols (**16**), can be obtained by use of LR via an indirect synthetic route (eq 25).[59] Also the transient pentafluorothiobenzaldehyde (**17**) can be prepared with LR and trapped as the anthracene cycloadduct, from which it can be regenerated by pyrolysis (eq 26).[60]





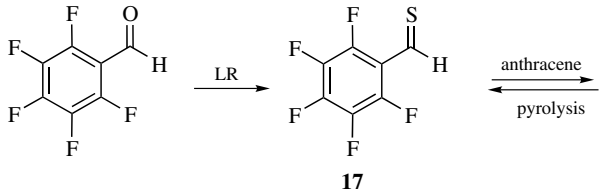
(24)

14 **15**



(25)

16



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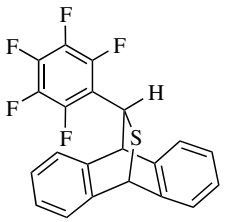
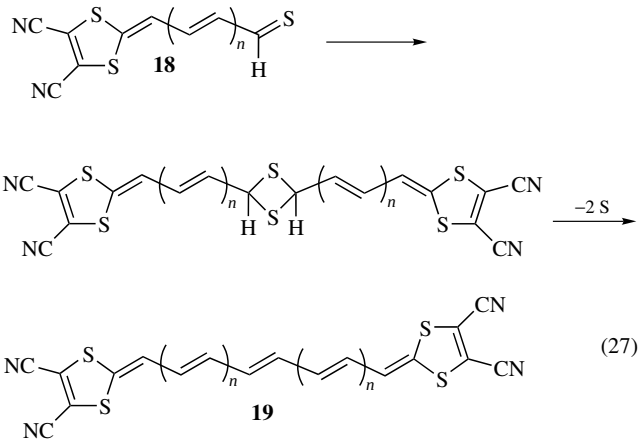


(26)

The thioaldehydes (**18**) are obtained from the corresponding aldehydes with, LR. They dimerize spontaneously to yield 1,3-dithietanes, which extrude sulfur to give the interesting polymethinetetrathiafulvalenes (**19**) (eq 27).[61]



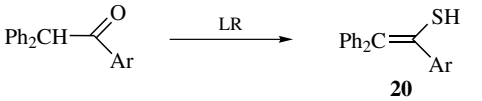
(27)

18 **19**

Thionation of Ketones. The synthesis of thioketones from ketones by use of LR was described decades ago but several new review articles on this fundamental reaction have been published in recent years.[46,47,50,62–64]

Varma and Kumar have considerably improved the protocol for thionation reactions with LR.[65] The reactions are run without a solvent under microwave irradiation. Only 0.5 equiv of LR are required and the thioketones are produced with over 95% yield within a reaction time of only 3 min. Improved yields, e.g., 96% of 4,4′-dimethoxythiobenzophenone, are also achieved by thionation at room temperature with the "solubilized" reagent (**13**).[48]

The formation of dibenzobicyclo[2,2,2]octanethione and the enethiol (**16**) has already been mentioned.[59] The related stable enethiol (**20**) can be obtained directly from the corresponding ketone and LR (eq 28).[58]

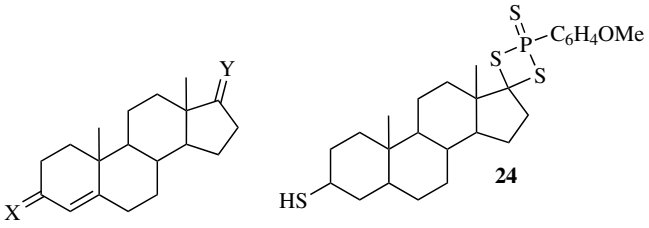


(28)

20

In the same way, 10-methylsulfanylbornane-2-thione has been prepared.[66] The reaction of androst-4-ene-3,17-dione (**21**) with LR in toluene gave the mono- (**22**) and the bisthione (**23**), whereas

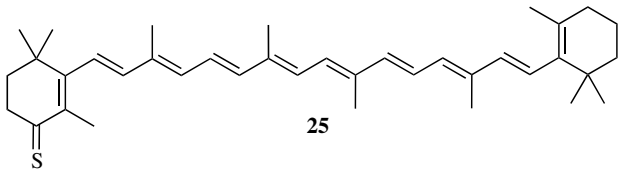
other steroidal ketones led to complex phosphorus-sulfur heterocycles such as **24**, which exhibits antimicrobial and antifungal activity.[67]



24

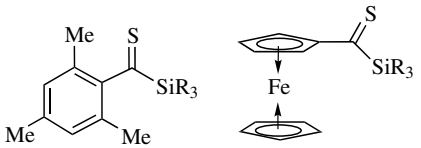
21: X = Y = O
22: X = O, Y = S
23: X = Y = S

Carotinoid thioketones, e.g., β,β-carotene-4-thione (**25**), are obtained by thionation of the corresponding ketones with LR in benzene at 40 °C but not in other solvents.[68]



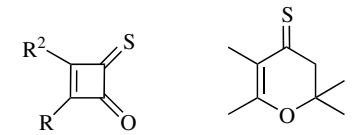
25

Whereas most silylthioketones are too labile to withstand the rather harsh standard reaction conditions normally applied in reactions with, LR, sterically protected mesityl derivatives (**26**)[69] and the ferrocenyl silyl thioketones (**27**)[70] can be obtained from the corresponding ketones and LR with good yields.



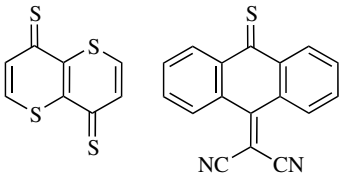
26 **27**

Stable thiocarbonyl compounds (**28**)[71] are formed regioselectively from the corresponding squaric and semisquaric acid derivatives. On the other hand, α-oxo-thioamides are further thionated to yield α-thioxo-thioamides.[14,72,73] The thioketones (**29**),[74] (**30**),[75] and (**31**)[76] are obtained by reaction of the cyclic enones or 10-(dicyanomethylene)-9-anthrone with LR in toluene.



28 R^1 = OR, NR_2
R^2 = OEt, Ar,Bu

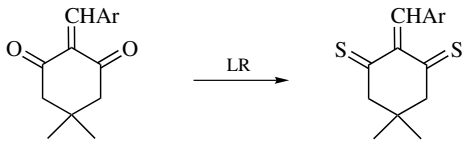
29



30

31

Squarylium dyes react with LR to yield the corresponding 1,3-dithiosquarylium dyes, which exhibit a characteristic bathochromic shift of 25 nm compared with the squarylium compounds.[77] Arylidenedimedones are transformed into the corresponding dithiones (**32**) by use of LR (eq 29),[78] whereas reaction of the methylenetetralones (**33**) with LR led to the followup products (**34**) and (**35**) of the expected thione (eq 30).[79]



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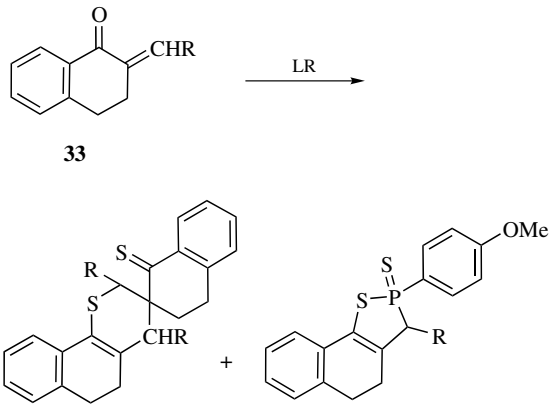
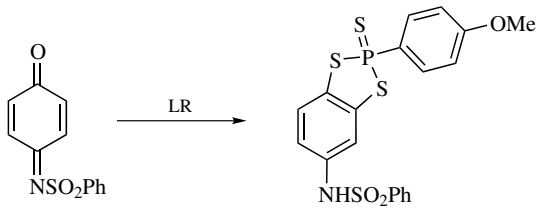


(30)

34 **35**

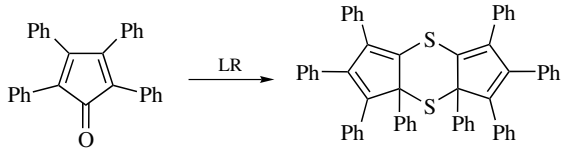
The quinone monoimine (**36**) reacts with LR to yield the 1,3,2-dithiaphosphole 2-sulfide (**37**) (eq 31), whereas phenoxathiines are formed with phosphorus pentasulfide.[80]



(31)

36 **37**

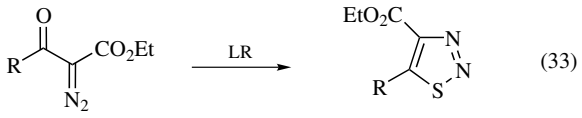
Tetraphenylcyclopentadienethione, which obviously represents the primary product of the reaction of tetraphenylcyclopentadienone (**38**) with, LR, spontaneously dimerizes with phenyl group migration to form the 1,4-dithiin (**39**) (eq 32).[81]



(32)

38 **39**

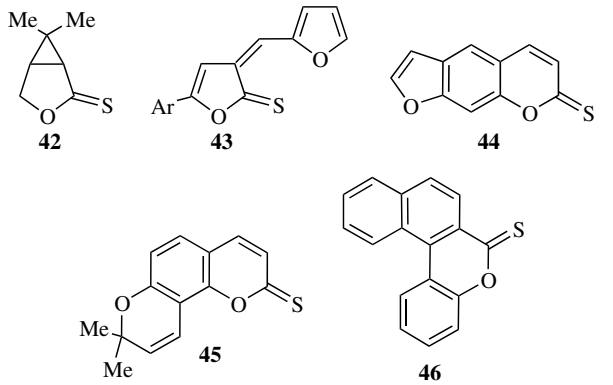
β-Oxo-α-diazocarboxylic esters (**40**) are transformed into 1,2,3-thiadiazoles (**41**) (eq 33). These represent the valence tautomers of the corresponding α-diazo-β-thioxo esters, which, however, cannot be detected as the intermediate products.[82,83]



40 **41** (33)

Thionation of Carboxylate Esters and Lactones. The reaction of esters and lactones with LR represents a well-established method for the synthesis of the corresponding thiocarbonyl derivatives.[46,84–86] In fact, LR is the much superior reagent for the thionation of esters as compared with phosphorus pentasulfide. Open-chain thionoesters have been conveniently obtained.[87,88] Interestingly, natural triglycerides also smoothly react with LR to yield pure tristhionotriglycerides.[89] Even better results are obtained with carboxylate esters if the improved "solubilized" LR[48] or microwave irradiation[65] are applied. The method has particularly been used for the preparation of cyclic thionoesters. Obviously there are very few structural or other restrictions that inhibit the formation of γ-,δ-, or macrocyclic thionolactones. Once more, microwave irradiation significantly improves the results.[65,90]

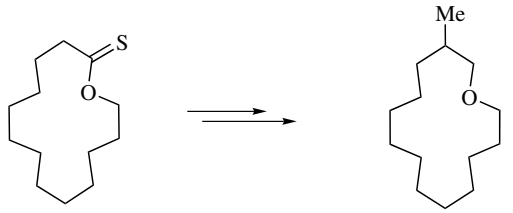
The 2,3-cyclopropano-γ-thionolactone (**42**) has been studied with respect to its chiroptical properties.[91] The 2,3-dihydrofuran-2-thione (**43**),[92] thionophthalide derivatives,[93,94] thiocoumarins[95–98] including the physiologically active thionopsoralene (**44**),[95] the precursor (**45**) of the prospective *anti*-HIV drug di-*O*-camphanoyl-thionokhellactone,[99] and the tetracyclic δ-thionolactone (**46**)[100] have been obtained from the corresponding lactones by use of LR.



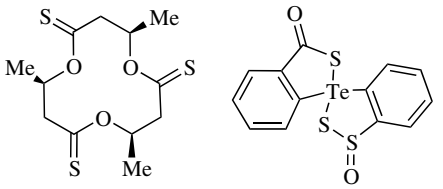
42 **43** **44** **45** **46**

In the 1995 Nicolaou[27,101] total synthesis of brevetoxin B thionolactone preparation with LR plays a deciding role. The 14-membered thionolactone (**47**) has been prepared from the lactone and then transformed into the ether (**48**) by methylation and reduction with tributyltin hydride (eq 34).[102] The tristhionotriolide (**49**) was formed besides the mono- and the bisthiono derivative when the triolide reacted with LR, whereas only up to three thiocarbonyl groups could be introduced into the corresponding pentolide.[103] A spirotellurane-bisthionolactone was only formed as a transient intermediate, which spontaneously rearranged to the more stable bisthiololactone (**50**).[104]

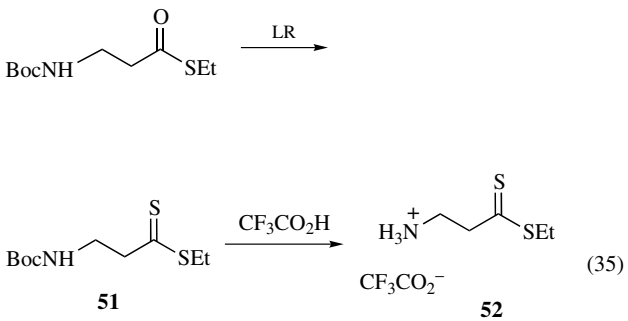
Dithiocarboxylate esters and dithiolactones are analogously available from thioloesters or thiololactones and LR.[84,86] Open-chain aryl phenyldithioacetates,[105] 1-arylethyl arenedithioates,[106] and also ethyl *N*-Boc-β-aminopropanedithioate (**51**) have been obtained from the thioloesters. Deprotection of **51** led to the dithio-β-alanine ester salt (**52**) (eq 35).[107]



47 **48** (34)

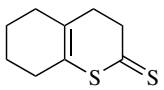


49 **50**



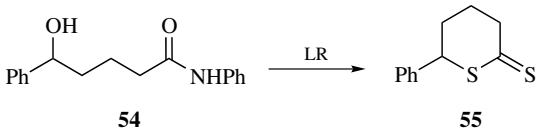
51 **52** (35)

Dithio-γ-lactones,[108,109] dithiophthalides,[110] as well as the hexahydrodithiocoumarin (**53**) are readily obtained from the thiololactone precursors and LR but only decomposition is observed when a reaction between LR and a six-membered δ-thiololactone is attempted (see above).



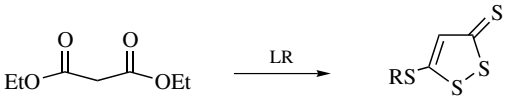
53

One can, however, prepare the δ-dithiolactone (**55**) from the open-chain ω-hydroxyamide (**54**) and LR, which acts as a thionation and cyclization (condensation) reagent in this case (eq 36).[111]



54 **55** (36)

Diethyl malonate and the dihydroxydicarboxylic ester (**57**) yield the 1,2-dithiole-3-thiones (**56**)[112] and (**58**) [$(CS)_8$],[113] which can be conceived as dithiolactones as well (eqs 37 and 38).



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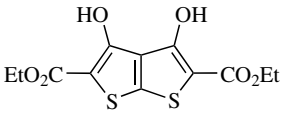
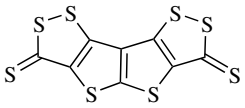
56



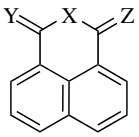
57



(38)

58

Besides the esters, carboxylic and thiocarboxylic anhydrides react with LR to form thiono- and dithiocarboxylic anhydrides.[84,85] In particular, the dithio- and trithio-1,8-naphthalic anhydrides (**60**)–(**62**) have been prepared from the anhydride (**59**).[114]

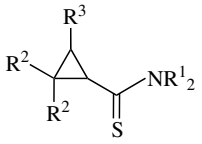


59: X = Y = Z = O
60: X = O, Y = Z = S
61: X = Y = S, Z = O
62: X = Y = Z = S

Thionation of Amides and Peptides. The transformation of carboxamides into the corresponding thioamides is, of course, an established standard reaction of LR.[46,115,116] It has been applied now as before in many cases since application of the simpler alternative, phosphorus pentasulfide, exhibits several drawbacks. In particular, "during the last two decades, the importance of LR as thionating reagent for amino acids and peptides has grown significantly."[46] Frequently the formation of followup products is observed besides the mere conversion of an amide into a thioamide function. As expected, this occurs when amides bearing a second functional group are used as starting compounds and the reactions end up with the formation of heterocycles. An example (**55**) has already been mentioned above. The formation of heterocycles will be treated in more detail in the next section, although one cannot always strictly separate this aspect of chemistry from the simpler type of reaction.

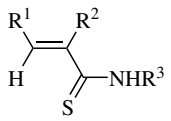
Several improvements of the method have been introduced. The solvent-less, microwave-assisted protocol of Varma and Kumar[65] works well with amides too. It has been further developed and applied for a very efficient parallel synthesis of thioamide libraries.[117] The thionation of different types of amides in anhydrous THF at temperatures below 80 °C has turned out to be advantageous.[118] Also the modified reagent (**13**) has been successfully used.[48]

A variety of carboxamides not carrying further functionalities has been transformed into the corresponding thiocarboxamides by the use of LR,[48,119] including the cyclopropane derivatives (**63**),[120] dithiooxamide,[121] *N*,*N*′-disubstituted dimethylmalonic acid bisthioamides,[122] the dibenzo[16]crown ether thioamides (**66**),[123] and the calix[4]arene thioamide **67**.[124] Also the somewhat labile unsaturated derivatives of the acryloyl- (**64**)[125] and the enamide-type (**65**)[126] have been successfully prepared by the use of LR.



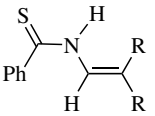
63

R^1 = Me/Me, H/Bu
R^2 = H/Ph, Cl/Cl
R^3 = H, Me, Alk

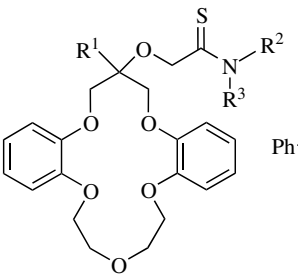


64

R^1 = H, Me, Ph
R^2 = H, Me
R^3 = Alk, Ph

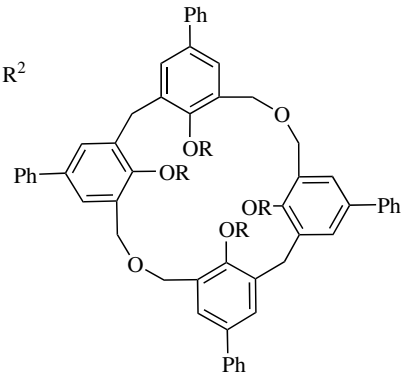


65



66

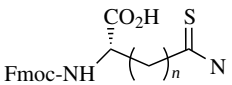
R^1 = H, Pr
R^2 = H, Me
R^3 = H, Me, Alk



67

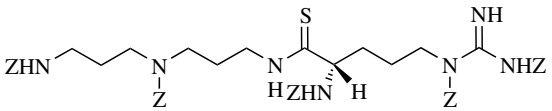
R = CH_2-CS-NEt_2

Reactive functional groups withstand reactions with LR if proper conditions are chosen. The thionation of *N*-(*ω*-haloalkyl) amides with 0.5 equiv of LR yields the corresponding thioamides without attack at the halo substituent.[127] Optically pure *ω*-thioamides of Fmoc-asparagic and -glutamic acid (**68**) have been prepared with another LR analog, *O*,*O*-bis(*tert*-butyldimethylsilyl)-4-methoxybenzenephosphonothioate [*p*-MeO-C_6H_4-P(S)(OTBDMS)$_2$].[128] The protected polyamine thioamide (**69**) is related to the spider toxin FTX.[129]



68

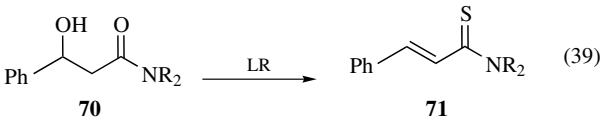
n = 1, 2



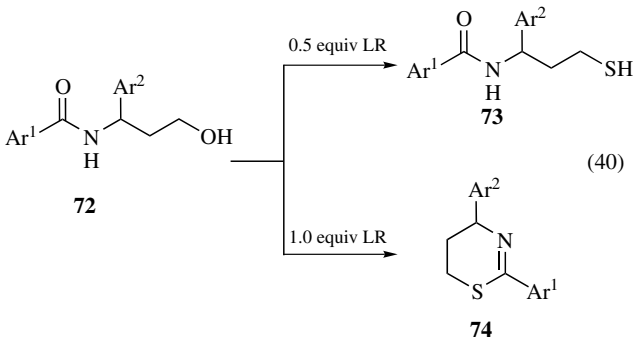
69

Nishio et al. have systematically studied the thionation of hydroxy- and ketothioamides. They have established the following order of decreasing reactivity toward LR: alcohol > amide > ketone > ester, which can be used for chemoselective reactions.[130] *N*,*N*-Disubstituted 3-hydroxy-3-phenyl-propanamides (**70**) are

thionated and simultaneously dehydrated to yield α,β-unsaturated thioamides (**71**), whereas the corresponding anilides form γ-dithiolactones (eq 39).[111,130] The *N*-thiobenzoylenamines (**65**) are formed by treatment of the corresponding *N*-benzoyl-2-aminoalkanols with LR.[126] *N*-Acyl-3-aminoalkanols (**72**), on the other hand, exclusively give 4*H*-5,6-dihydro-1,3-thiadiazines (**74**) with equimolar amounts, but *N*-acyl-3-aminoalkanethiols (**73**) with 0.5 equiv of LR (eq 40).[132]

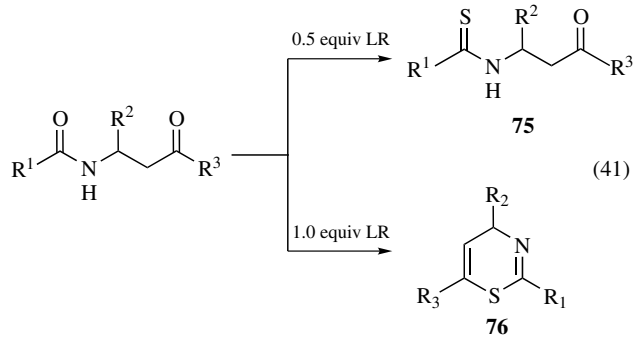


70 **71** (39)

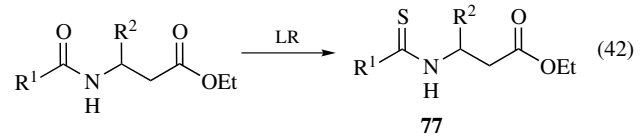


72 **73** **74** (40)

The outcome of the treatment of *N*-3-oxoalkylamides again depends of the amount of LR applied. Mainly the open-chain thioamides (**75**) are formed with 0.5 equiv, while 4*H*-1,3-thiazines (**76**) are the predominant products if 1.0 equiv is used (eq 41).[130,133] The amide moiety of ethyl *N*-benzoyl-3-aminopropanoates is selectively thionated to form the thioamides (**77**) (eq 42).[130,133]

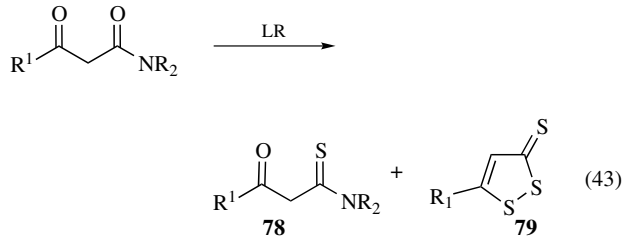


75 **76** (41)



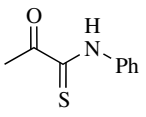
77 (42)

Mixtures of β-oxothioamides (**78**) and 1,2-dithiol-3-thiones (**79**) are formed from β-oxoamides (eq 43).[134]



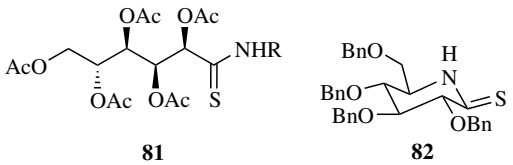
78 **79** (43)

Also, α-oxothioamides, e.g., 2-oxopropanethioanilide (**80**), are easily obtained with LR.[135]



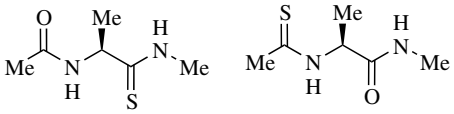
80

Starting from δ-gluconolactone the sugar-derived thioamide (**81**) can be obtained via thionation of the corresponding amide with LR.[136] The related thiolactam (**82**) was prepared from the lactam because a higher yield of the desired oxime could be achieved with (**82**).[137]

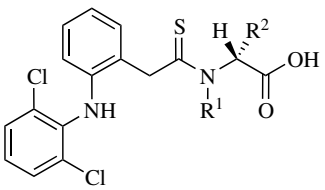


81 **82**

The two thionated *N*-acetyl-alanine-*N*-methylamides (**83**) and (**84**)[138] and also the more sophisticated *N*-phenylthioacetyl conjugates of unnatural amino acid (**85**)–(**88**) are obtained by the use of, LR. Compounds (**85**)–(**88**) are derivatives of the important antiinflammatory and analgesic drug diclofenac. The drug itself exhibits ulcerogenic side effects. These are not observed for the thioamides, which retain, however, the antiphlogistic activity of diclofenac. In particular, the sarcosine conjugate (**85**) represents, thus, a promising candidate for therapeutic applications.[139]



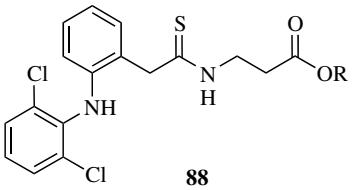
83 **84**



85: R^1 = Me, R^2 = H

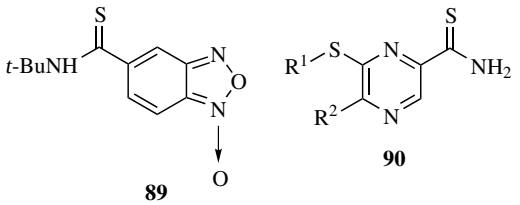
86: R^1 = H, R^2 = CH_2CHMe_2

87: R^1 = H, R^2 = CH_2Ph



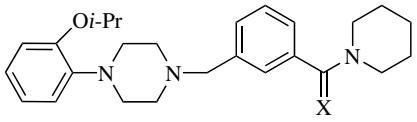
88

The secondary thioamide (**89**) is formed from the corresponding amide and LR without reduction of the *N*-oxide functionality.[140] Primary pyrazinecarbothioamides (**90**) prepared by the use of LR exhibit higher in vitro activities against *Mycobacterium tuberculosis* than the corresponding amides.[141] In the context of research aimed at the synthesis of new antipsychotic drugs, the thioanalog (**92**) of the active compound mazapertine (**91**) has been prepared with LR.[142]



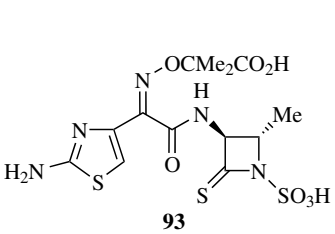
89

90

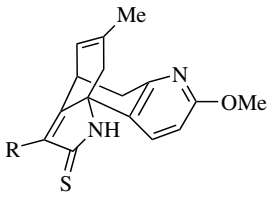


91: X = O (mazapertine)
92: X = S

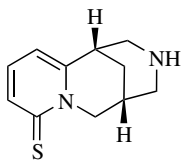
A diversity of thiolactams has been prepared from the corresponding lactams by use of LR[65] or of the modified reagent (**13**).[48] Monobactam analogs, e.g., the weakly antibacterial β-thiolactam (**93**), have been prepared by thionation of suitably protected optically active β-lactams with LR or Davy's reagent (2,4-bis (methylthio)-1,3,2,4-dithiadiphosphetane disulfide), deprotection and subsequent introduction of the side chain.[143] Very recently, an efficient solid-phase synthesis of 1,3,4-trisubstituted β-thiolactams has been described.[144] The γ-thiolactam (**94**) has been prepared as an intermediate for the synthesis of analogs of the acetylcholinesterase inhibitor huperzine B.[145] Transformation of the quinoline alkaloid cytisine into its thio analog (**95**) enhanced its biological activity.[146]



93

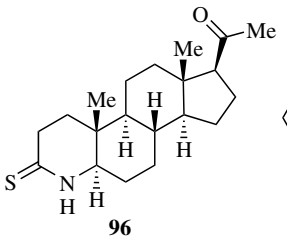


94: R = Me, Et

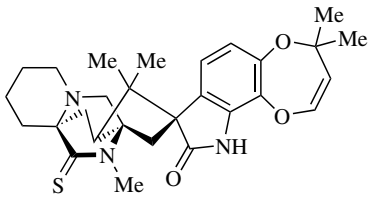


95 [(−)-thiocytisine]

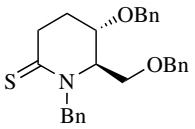
Six-membered δ-thiolactams represent by far the largest number of examples. The steroidal thiolactam (**96**) is formed chemoselectively.[147] The *N*-methyl-δ-lactam moiety of the antibiotic marcfortine A is selectively thionated to 18-thiomarcfortine A (**97**) while the unsubstituted γ-lactam group is not attacked by LR.[148] The optically active δ-thiolactam (**98**) is a useful intermediate for the total synthesis of the alkaloid prosopinine.[149]



96

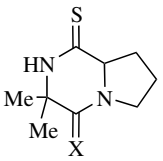


97

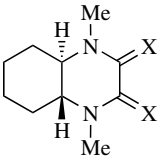


98

Perhydropyrrolo[1,2-*a*]pyrazine-1-thione (**99**) is formed chemoselectively on thionation of the dione with LR, whereas the 1,4-dithione (**100**) is obtained from the corresponding 4-thione.[150] Compound (**101**) yields the deep red colored dithione (**102**), which represents a dithiooxamide exhibiting the unusual *s-cis* configuration.[151]

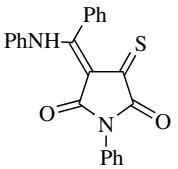


99: X = O
100: X = S

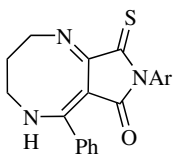


101: X = O
102: X = S

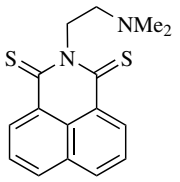
Selective thionation of *N*-arylmaleinimides[152] and pyrrolidine-2,3,5-trione derivatives[153] led to monothioimides such as **103**[153] and **104**.[153] The 1,8-dithionaphthalimide (**105**) resulted from the reaction of the naphthalimide with LR.[154]



103



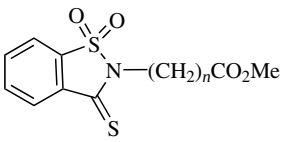
104



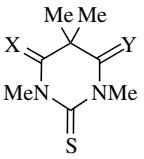
105

The *N*-substituted thiosaccharine derivatives (**106**) are formed with LR. The ester group is not attacked by LR and the yields are higher than those obtained with phosphorus pentasulfide.[155] 4-*N2*-Arylhydrazono-5-methylpyrazole-3-thiones have been prepared from the corresponding pyrazolones.[156] Thionation of the

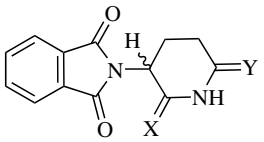
monothio barbituric acid (**107**) led both to the dithio (**108**) and trithio (**109**) derivatives.[157] Thiothalidomides (**111**) and (**112**) have been synthesized from thalidomide (**110**) with LR. The thioderivatives with an intact phthalimido moiety potently inhibited the tumor necrosis factor (TNF-α) secretion in contrast to **110** and represent promising candidates for clinical employment.[158]



106 n = 1, 2

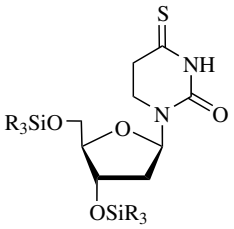


107: X = Y = O
108: X = O, Y = O
109: X = Y = S

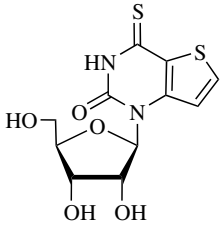


110: X = Y = O
111: X = O, Y = S
112: X = Y = S

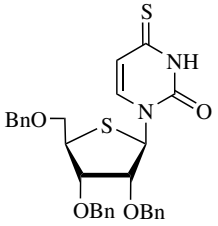
The purine bases, caffeine, theophylline, and theobromine, yield the corresponding 6-monothio- and 2,6-dithio derivatives upon reaction with LR without a solvent under microwave irradiation.[159] Thionation of the carbonyl groups in the nucleobases of nucleotides leads to interesting special types of thiolactams, which are expected to exhibit modified biological activities. Pyrimidine nucleosides are selectively thionated in the 4-position of the nucleobase. The mild reaction conditions applied allow the conversion of nucleosides with labile glycosidic bonds, such as 5,6-dihydropyrimidine-(**113**)[160,161] and 2′,3′-dideoxynucleosides.[161] Thiononucleosides with unnatural bases (**114**)[162] or sugar moieties (**115**),[163] (**116**)[164] can also be prepared.



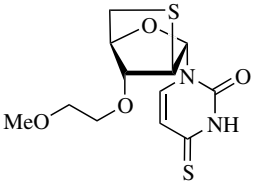
113



114

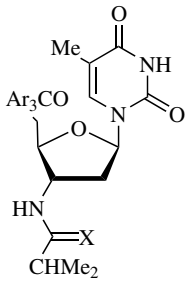


115

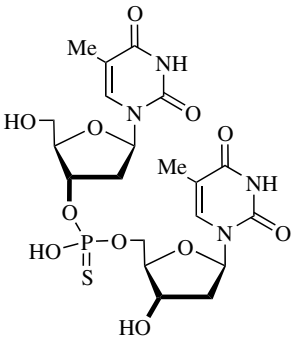


116

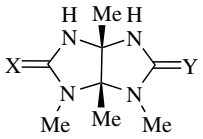
The 3′-isobutyroylamino-thymidine derivative (**117**), on the other hand, reacts with 1 equiv of LR in the side chain to form the thioamide (**118**).[165] Phosphite esters which are used as intermediates in solid-phase synthesis of oligonucleotides are converted into the corresponding phosphorothioates (**119**).[166] Interestingly, LR can also be used as a potent catalyst for the synthesis of nucleosides.[167] Tetramethylglycoluril (**120**) is readily converted to the monothiono- (**121**) or the dithionoglycoluril (**122**) depending on the applied molar amount of LR.[168]



117: X = O
118: X = S



119

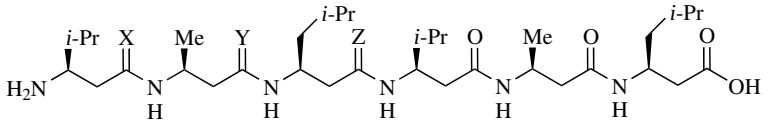


120: X = Y = O
121: X = O, Y = S
122: X = Y = S

Also, *N-iso*-propyl-thiobenzhydroxamic acid could be prepared from the corresponding hydroxamic acid by applying 0.5 equiv of LR in anhydrous THF as solvent.[169]

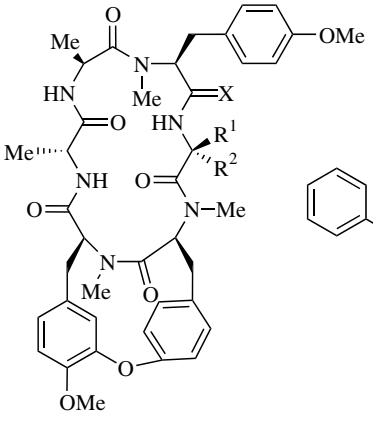
Endothiopeptides, alias peptide thioamides, represent a class of compounds of particular and increasing importance in modern peptide chemistry. A comprehensive, informative review of this topic has been published, in which it is clearly pointed out that thionation by use of LR obviously is the method of choice for the synthesis of endothiopeptides.[170] The advantages of LR as compared with phosphorus pentasulfide and other thionating reagents are dealt with in detail as well as rare drawbacks that can occur and precautions that have to be taken into account. Only some novel results will, therefore, be described here. The difficulties arising with attempts to react larger peptides with LR have been overcome by use of anhydrous dioxane as solvent. The cyclic peptides astin A, B, and C were selectively monothionated at the serinamide carbonyl group,[171] whereas the segetalins were transformed into dithiosegetalins.[172] The three thiohexapeptides (**123**)–(**125**) consisting only of β-amino acids have been prepared by stepwise application of LR for the introduction of sulfur into the molecule.[173]

The bicyclic hexapeptide RA-VII (**126**), an antitumor agent from rubia plants, has been selectively transformed into the thiopeptide (**127**). This was then cyclized to an oxazole, which was finally hydrolyzed to form [D-Ala-4]RA-VII (**128**), the epimer of (**126**).[174] Another bicyclic hexapeptide (**129**), which is a potent

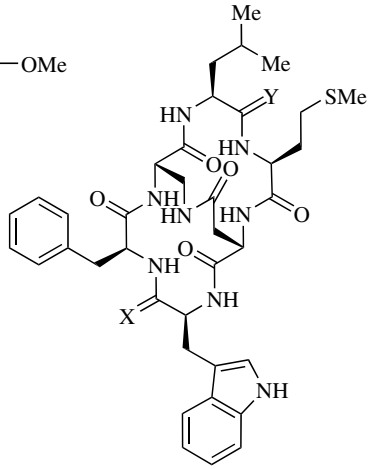


123: X = S, Y = Z = O
124: X = Y = S, Z = O
125: X = Y = Z = S

neurokinin A antagonist gave the two monothiopeptides (**130**) and (**131**) with LR.[175]



126: X = O, R^1 = Me, R^2 = H
127: X = S, R^1 = Me, R^2 = H
128: X = O, R^1 = H, R^2 = Me

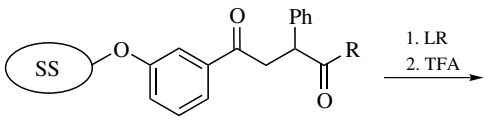


129: X = Y = O
130: X = O, Y = S
131: X = S, Y = O

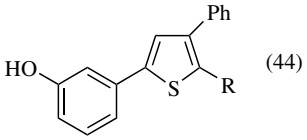
Formation of Heterocycles. LR has found widespread application in the synthesis of heterocycles. In particular, the formation of thiophenes and other sulfur heterocycles as well as nitrogen-containing sulfur heterocycles but also of compounds with sulfur and phosphorus [stemming from LR see, e.g. (**15**), (**24**), (**35**), (**37**)] has been achieved with LR, which has very advantageously replaced the classical reagent for this purpose, phosphorus pentasulfide. The respective literature until 2002 has been thoroughly evaluated by Jesberger et al.[46] in their 2003 review. Only a few supplementary papers and the more recent significant results are therefore treated here.

Thiophenes are generally obtained by sulfuration of 1,4-dicarbonyl compounds (Paal synthesis). The preparation of the highly substituted 2-(4-bromophenyl)-5-(3,4-dimethoxyphenyl)-3,4-dimethylthiophene from the respective 1,4-diketone represents a recent example.[176] This type of reaction can be performed as a solid-phase synthesis with polymer-bound diketones (**132**) and LR (eq 44). Trifluoroacetic acid releases the thiophene (**133**) from the solid support.[177] Bismuth triflate in 1,3-dialkylimidazolium fluoroborate has been utilized as a catalytic ionic liquid system for the synthesis of thiophenes from 1,4-diketones and LR with significantly improved yields.[178]

Bithiophenes with alkoxy or dialkylamino substituents in the 5-position (**135**) have been obtained from γ-oxobutanoic esters or amides (**134**) (eq 45).[179]

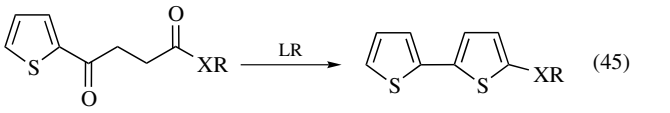


132 (SS = solid support)



(44)

133

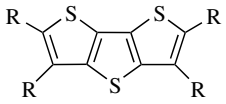


(45)

134

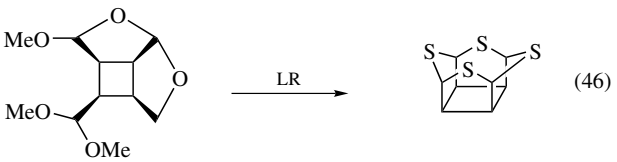
135: X = O, NR; R = Me, Et, *c*-Hex

Condensed thiophenes (**136**)[180] have also been obtained by use of LR.



136

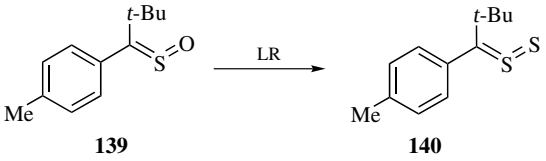
A 10% yield of the "thiabowl" (**138**)[181] was formed in a complex reaction from the tricyclic acetal (**137**) (eq 46).

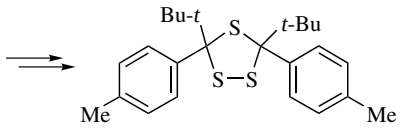


(46)

137 **138**

Thioketone *S*-oxides with pronounced steric hindrance such as the thiopivalophenone *S*-oxide (**139**) are thionated with LR to yield the corresponding *S*-sulfides (**140**) as elusive intermediates, which further react with a thione to afford the 1,2,4-trithiolane (**141**) (eq 47).[182]

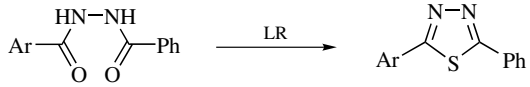




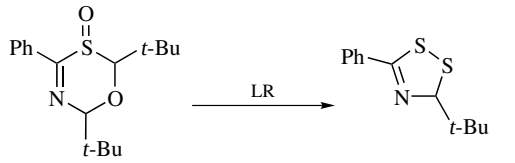
(47)

The formation of 1,2,3-thiadiazoles (**41**) has been mentioned above.[82,83] Their isomers, 1,3,4-thiadiazoles (**143**), are produced with good yields from 1,2-diacylhydrazines (**142**) (eq 48).[183] In a complicated redox reaction 1,2,4-dithiazoles (**145**) are formed from 6*H*-1,3,5-oxathiazine *S*-oxides (**144**) and LR at high temperatures (eq 49).[184]

Interestingly, the established reaction of phenylhydrazine with β-dicarbonyl compounds to form pyrazoles has been shown to be catalyzed by LR. No sulfur is incorporated into the final product. Thus, a 95% yield of 5-*N*,*N*-diethylamino-3-methyl-1-phenylpyrazole is obtained under mild reaction conditions from *N*,*N*-diethylacetoacetamide in the presence of LR.[185]

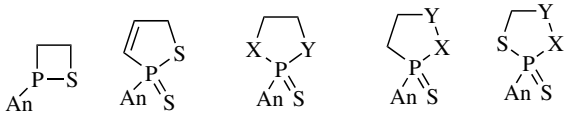


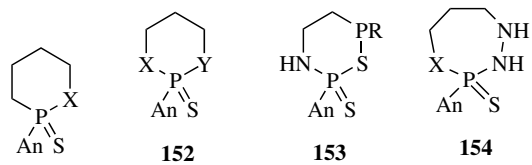
(48)



(49)

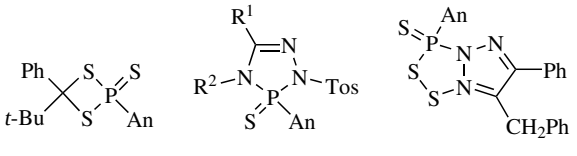
The formation of four- (**146**), five- (**147**)–(**150**), six- (**151**)–(**153**), and seven-membered (**154**) heterocycles, in which not only sulfur but also phosphorus together with the *p*-methoxyphenyl substituent (An) of LR are incorporated into the ring, has been comprehensively reviewed.[46]

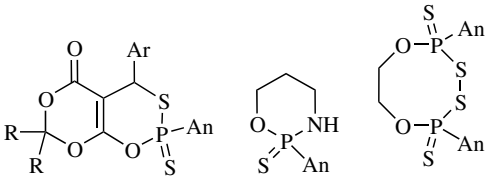




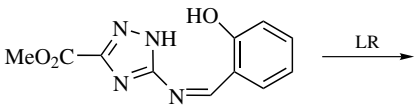
Recently, additional examples of type (**148**),[186] (**150**),[187–189] (**151**),[190] and (**152**)[187–193] have been described. Also, several compounds with a novel pattern of heteroatoms in the ring have been obtained from suitable starting compounds. Treatment of sterically hindered thioketones with LR gave 1,3,2-dithiaphosphetane 2-sulfides (**155**) as mixtures of the two diastereoisomers.[194] The 1,2,4,3-triazaphosphole 3-sulfide (**156**) is obtained from *N1*-tosylamidrazones and LR.[195] The bicyclic pyrazolo[2,3-*d*]-1,2,4,3-dithiaazaphosphole (**157**) is formed by reaction of 4-benzyl-5-phenylpyrazolone with LR.[192] The six-membered 1,3,2-oxathiaphosphinines (**158**)[192] and 1,3,2-oxazaphosphinines (**159**)[186,193] are achieved from cyclic arylidenemalonates and 2-aminobenzamides or β-aminopropionitriles, respectively.

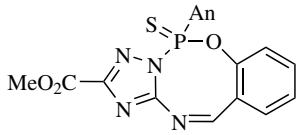
Both hydroxy groups of ethane-1,2-diol and related diols readily react with LR and the resulting bisdithiophosphonates can be cyclized by oxidation with iodine to form the eight-membered heterocycle (**160**).[196]





Another eight-membered phosphorus heterocycle, the oxadiazaphosphocine (**162**) is formed from the 1,5-amino-hydroxy compound (**161**) and LR (eq 50).[197]

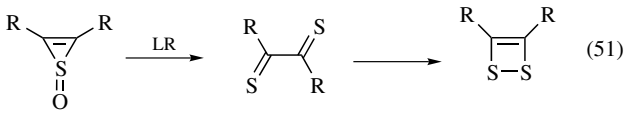




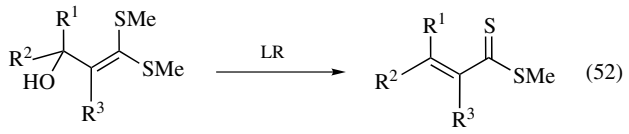
(50)

Miscellaneous Reactions. In certain cases, unexpected reactions occur with LR. The formation of the thiophosphate (**119**) from the corresponding phosphite[166] has already been mentioned. Similarly, dimethyl thiophosphite can be obtained from dimethyl phosphite.[198] Heterocyclic halobenzyl alcohols are deoxygenated by LR under microwave irradiation in the presence of molybdenum hexacarbonyl as catalyst without concomitant dehalogenation.[199] Thiirene-1-oxides with bulky substituents (**163**, R = *tert*-butyl, 1-adamantyl) are reduced and thionated under

ring opening to form the 1,2-dithiones (**164**), which rearrange to the corresponding dithietes (**165**) (eq 51).[200] The ketenedithioacetals (**166**) eliminate methanol under formation of methyl dithioacrylates (**167**) upon reaction with LR (eq 52).[201]



163 **164** **165**



166 **167**

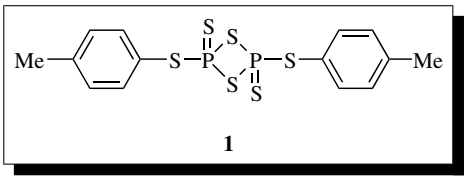
1. (a) Cherkasov, R. A.; Kutyrev, G. A.; Pudovik, A. N., *Tetrahedron* **1985**, *41*, 2567. (b) Cava, M. P.; Levinson, M. I., *Tetrahedron* **1985**, *41*, 5061. (c) Aldrich Library of Infrared Spectra; Aldrich Chemical Co.: Milwaukee, 1985; Vol. 1(2), p 557B.
2. Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O., *Org. Synth.*, **1984**, *62*, 158.
3. Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O., *Bull. Soc. Chim. Belg.* **1978**, *87*, 223.
4. Sato, M.; Asai, M., *J. Organomet. Chem.* **1992**, *430*, 105.
5. Klages, C.-P.; Voss, J., *Chem. Ber.* **1980**, *113*, 2255.
6. Wenck, H.; de Meijere, A.; Gerson, F.; Gleiter, R., *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 335.
7. Scheibye, S.; Shabana, R.; Lawesson, S.-O.; Rømming, C., *Tetrahedron* **1982**, *38*, 993.
8. Kametani, S.; Ohmura, H.; Tanaka, H.; Motoki, S., *Chem. Lett.* **1982**, 793.
9. (a) Walter, W.; Proll, T., *Synthesis* **1979**, 941. (b) Shabana, R.; Rasmussen, J. B.; Olesen, S. O.; Lawesson, S.-O., *Tetrahedron* **1980**, *36*, 3047. (c) Rasmussen, J. B.; Shabana, R.; Lawesson, S.-O., *Tetrahedron* **1982**, *38*, 1705. (d) Pulst, M.; Greif, D.; Kleinpeter, E., *Z. Chem.* **1988**, *28*, 345.
10. Kühn, R.; Otto, H.-H., *Arch. Pharm. (Weinheim, Ger.)* **1989**, *322*, 375.
11. Weiss, D.; Gaudig, U.; Beckert, R., *Synthesis* **1992**, 751.
12. Muzaffar, A.; Brossi, A., *Synth. Commun.* **1990**, *20*, 713.
13. El-Kateb, A. A.; Hennawy, I. T.; Shabana, R.; Osman, F. H., *Phosphorus Sulfur/Phosphorus Sulfur Silicon* **1984**, *20*, 329.
14. Adiwidjaja, G.; Günther, H.; Voss, J., *Liebigs Ann. Chem.* **1983**, 1116.
15. Köpke, B.; Voss, J., *J. Chem. Res. (S)* **1982**, 314.
16. Strehlow, T.; Voss, J.; Spohnholz, R.; Adiwidjaja, G., *Chem. Ber.* **1991**, *124*, 1397.
17. Ishii, A.; Nakayama, J.; Ding, M.; Kotaka, N.; Hoshino, M., *J. Org. Chem.* **1990**, *55*, 2421.
18. Voss, J., *Comprehensive Organic Synthesis* **1991**, *6*, 435.
19. Jones, B. A.; Bradshaw, J. S., *Chem. Rev.* **1984**, *84*, 17.
20. Pedersen, B. S.; Scheibye, S.; Clausen, K.; Lawesson, S.-O., *Bull. Soc. Chim. Belg.* **1978**, *87*, 293.
21. Scheibye, S.; Kristensen, J.; Lawesson, S.-O., *Tetrahedron* **1979**, *35*, 1339.
22. Takano, S.; Tomita, S.; Takahashi, M.; Ogasawara, K., *Synthesis* **1987**, 1116.
23. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R., *J. Am. Chem. Soc.* **1990**, *112*, 6263.
24. Baxter, S. L.; Bradshaw, J. S., *J. Org. Chem.* **1981**, *46*, 831.
25. Smith, C.; Tunstad, L. M.; Guttierrez, C. G., *Phosphorus Sulfur Silicon* **1988**, *37*, 257.
26. Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P., *J. Am. Chem. Soc.* **1990**, *112*, 3040.
27. Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, Xiao-Yi; Hwang, C.-K., *J. Am. Chem. Soc.* **1993**, *115*, 3558.
28. Ghattas, A.-B. A. G.; El-Khrisy, E.-E. A. M.; Lawesson, S.-O., *Sulfur Lett.* **1982**, *1*, 69.
29. Oparin, D. A.; Kuznetsova, A. S., *Vestsi Akad. Navuk BSSR, Ser. Khim. Navuk* **1990**, *(6)*, 109. (*Chem. Abstr.* **1991**, *115*, 29 039y).
30. Hoederath, W.; Hartke, K., *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 938.
31. Shapiro, G.; Floersheim, P.; Boelsterli, J.; Amstutz, R.; Bolliger, G.; Gammenthaler, H.; Gmelin, G.; Supavilai, P.; Walkinshaw, M., *J. Med. Chem.* **1992**, *35*, 15.
32. Lakshmikantham, M. V.; Chen, W.; Cava, M. P., *J. Org. Chem.* **1989**, *54*, 4746.
33. Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O., *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.
34. Shabana, R.; Scheibye, S.; Clausen, K.; Olesen, S. O.; Lawesson, S.-O., *Nouv. J. Chim.* **1980**, *4*, 47.
35. Khalid, M.; Vallée, Y.; Ripoll, J.-L., *Chem. Ind. (London)* **1988**, 123.
36. Kohrt, A.; Hartke, K., *Liebigs Ann. Chem.* **1992**, 595.
37. Verkoyen, C.; Rademacher, P., *Chem. Ber.* **1985**, *118*, 653.
38. Thorsen, M.; Yde, B.; Pedersen, U.; Clausen, K.; Lawesson, S.-O., *Tetrahedron* **1983**, *39*, 3429.
39. Sherman, D. B.; Spatola, A. F., *J. Am. Chem. Soc.* **1990**, *112*, 433.
40. Brown, D. W.; Campbell, M. M.; Chambers, M. S.; Walker, C. V., *Tetrahedron Lett.* **1987**, *28*, 2171.
41. Eberle, M. K.; Nuninger, F., *J. Org. Chem.* **1993**, *58*, 673.
42. Nishio, T., *J. Chem. Soc., Chem. Commun.* **1989**, 205.
43. Nugara, P. N.; Huang, N.-Z.; Lakshmikantham, M. V.; Cava, M. P., *Heteroatom. Chem.* **1991**, *32*, 1559.
44. Harris, P. A.; Jackson, A.; Joule, J. A., *Sulfur Lett.* **1989**, *10*, 117.
45. Bartsch, H.; Erker, T., *Tetrahedron Lett.* **1992**, *33*, 199.
46. Jesberger, M.; Davis, T. P.; Barner, L., *Synthesis* **2003**, 1929.
47. Li, Y.-G.; Zhu, X.-F.; Zhou, H.-J., *Youji Huaxue* **1995**, *15*, 461., *Chem. Abstr.* **1995**, *123*, 338589.
48. Foreman, M. S. J.; Slawin, A. M. Z.; Woollins, J. D., *Heteroatom. Chem.* **1999**, *10*, 651.
49. Collier, S. J. In *Science of Synthesis*; Vol. 27, Padwa, A., Ed.; Chapter 5. Thieme: Stuttgart, 2004, 177, esp. 186ff.
50. Dabdoub, M. J. In *Science of Synthesis*; Vol. 27, Padwa, A., Ed.; Chapter 6. Thieme: Stuttgart, 2004, 215, esp. 219ff.
51. (a) Grossmann, G.; Ohms, G.; Krüger, K.; Jeschke, G.; Jones, P. G.; Fischer, A., *Phosphorus Sulfur Silicon* **1995**, *107*, 57. (b) Ohms, G.; Fleischer, U.; Kaiser, V., *J. Chem. Soc., Dalton Trans.* **1995**, 1297.
52. Beckmann, H.; Grossmann, G.; Ohms, G.; Sielers, J., *Heteroatom. Chem.* **1994**, *5*, 73.
53. (a) Grossmann, G.; Ohms, G.; Krüger, K., *Phosphorus Sulfur Silicon* **1996**, *109–110*, 59. (b) Wu, G.; Wasylishen, R. E., *Solid State Nucl. Magn. Reson.* **1994**, *4*, 47., *Chem. Abstr.* **1995**, *123*, 24409.
54. Nakai, T.; McDowell, C. A., *Solid State Nucl. Magn. Reson.* **1995**, *4*, 163., *Chem. Abstr.* **1995**, *123*, 130662.
55. Yoshifuji, M.; An, D.-L.; Toyota, K.; Yasunami, M., *Tetrahedron Lett.* **1994**, *35*, 4379.
56. Shabana, R.; Yakout, E. M.; Atrees, S. S., *Heteroatom. Chem.* **1993**, *4*, 491.

57. He, L.; Cai, F.; Li, K., *Huaxue Shiji* **1999**, *21*, 22., *Chem. Abstr.* **1999**, *130*, 325163.
58. Selzer, T.; Rappoport, Z., *J. Org. Chem.* **1996**, *61*, 5462.
59. Valleé, Y.; Khalid, M.; Ripoll, J.-L.; Hakiki, A., *Synth. Commun.* **1993**, *23*, 1267.
60. Hasserodt, J.; Pritzkow, H.; Sundermeyer, W., *Chem. Ber.* **1993**, *126*, 1701.
61. Märkl, G.; Aschenbrenner, N.; Baur, A.; Rastorfer, C.; Kreitmeier, P., *Helv. Chim. Acta* **2003**, *86*, 2589.
62. McGregor, W. M.; Sherrington, D. C., *Chem. Soc. Rev.* **1993**, *22*, 199.
63. Whittingham, W. G. In *Comprehensive Organic Functional Group Transformations*; Katrizky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Vol. 3, Pergamon: Oxford 1995, 329, esp. 346.
64. Landais, Y.; Vincent, J. M. In *Science of Synthesis*; Vol. 26, Cossy, A., Ed.; Chapter 4.2. Thieme: Stuttgart, 2004, 647, esp. 699.
65. Varma, R. S.; Kumar, D., *Org. Lett.* **1999**, *1*, 697.
66. Montenegro, E.; Echarri, R.; Claver, C.; Castillón, S.; Moyano, A.; Pericàs, M. A.; Riera, A., *Tetrahedron: Asymmetry* **1996**, *7*, 3553.
67. (a) Mohamed, N. R.; Elmegeed, G. A.; Younis, M., *Phosphorus Sulfur Silicon* **2003**, *178*, 2003. (b) Wagner, K.; Weiß, D.; Beckert, R., *Synthesis* **1995**, 1245.
68. Sliwka, H.-R.; Liaaen-Jensen, S., *Acta Chem. Scand.* **1994**, *48*, 679.
69. Bonini, B. F., *Phosphorus Sulfur Silicon* **1993**, *74*, 31.
70. Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G., *Tetrahedron Lett.* **1999**, *40*, 6473.
71. Müller, M.; Heileman, M. J.; Moore, H. W.; Schaumann, E.; Adiwidjaja, G., *Synthesis* **1997**, 50.
72. Marchand, É.; Morel, G., *Bull. Soc. Chim. Fr.* **1996**, *133*, 903.
73. Zou, J.-P.; Zeng, R. S.; Wang, A.-F.; Lu, Z.-E., *Gaodeng Xuexiao Huaxue Xuebao* **1998**, *19*, 1771., *Chem. Abstr.* **1999**, *130*, 139306.
74. Obrecht, D.; Zumbrunn, C.; Müller, K., *J. Org. Chem.* **1999**, *64*, 6182.
75. Hemmerling, M.; Hünig, S.; Kemmer, M.; Peters, K., *Eur. J. Org. Chem.* **1998**, 1989.
76. Itoh, T.; Fujikawa, K.; Kubo, M., *J. Org. Chem.* **1996**, *61*, 8329.
77. Kim, S. H.; Han, S. K.; Kim, J. J.; Hwang, S. H.; Yoon, C. M.; Keum, S. R., *Dyes Pigm.* **1998**, *39*, 77., *Chem. Abstr.* **1998**, *129*, 332105.
78. Mohamed, N. R., *Phosphorus Sulfur Silicon* **2000**, *161*, 123.
79. Hegab, M., *Phosphorus Sulfur Silicon* **2000**, *166*, 137.
80. Boulos, L. S.; Hennawy, I. T.; Arsanious, M. H. N., *Heteroatom. Chem.* **1994**, *5*, 27.
81. Henriksen, M.; Hazell, R. G.; Larsen, F. K.; Schultz, T.; Sylvester-Hvid, K. O.; Klabunde, K. J.; Mikkelsen, K. V.; Senning, A., *Acta Chem. Scand.* **1998**, *52*, 950.
82. Wilkins, D. J.; Bradley, P. A. In *Science of Synthesis*; Store, R. C.; Gilchrist, T. L., Eds.; Chapter 13.9. Thieme: Stuttgart, 2004, Vol. 13, p 253.
83. In this case 2,4-bis(4-phenoxyphenyl)-1,3,2,4-dithiadiphosphetane disulfide was used instead of, LR Ohno, M.; Itoh, M.; Ohashi, T.; Eguchi, S., *Synthesis* **1993**, 793.
84. Ishii, A.; Nakayama, J., *Top. Curr. Chem.* **2005**, *251*, 183.
85. Ishii, A.; Nakayama, J. In *Comprehensive Organic Functional Group Transformations*; Katrizky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Pergamon: Oxford, 1995, p 506.
86. Metzner, P., *Top. Curr. Chem.* **1999**, *204*, 127.
87. Castro, E. A.; Ibáñez, F.; Santos, J. G.; Ureta, C., *J. Org. Chem.* **1993**, *58*, 4908.
88. Rozen, S.; Mishani, E., *J. Chem. Soc., Chem. Commun.* **1993**, 1761.
89. Eychenne, V.; Mouloungui, Z., *J. Am. Oil Chem. Soc.* **2001**, *78*, 229., *Chem. Abstr.* **2001**, *135*, 34567.
90. Filippi, J.-J.; Fernandez, X.; Lizzani-Cuvelier, L.; Loiseau, A.-M., *Tetrahedron Lett.* **2003**, *44*, 6647.
91. Milewska, M. J.; Gdaniec, M.; Połoński, T., *Tetrahedron: Asymmetry* **1996**, *7*, 3169.
92. Hamad, A.-S. S.; Hashem, A. I.; El-Kafrawy, A. F.; Saad, M. M., *Phosphorus Sulfur Silicon* **2000**, *159*, 157.
93. Bailey, J. H.; Coulter, C. V.; Pratt, A. J.; Robinson, W. T., *J. Chem. Soc., Perkin Trans. 1* **1995**, 589.
94. Nishio, T., *J. Chem. Soc., Perkin Trans. 1* **1995**, 561.
95. Becker, R. S.; Chakravorti, S.; Gartner, C. A.; De Graca Miguel, M., *J. Chem. Soc. Faraday Trans.* **1993**, *89*, 1007.
96. Iwanaga, H.; Naito, K.; Sunohara, K.; Okajima, M., *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1719.
97. Kumar, S.; Singh, B. K.; Kalra, N.; Kumar, V.; Kumar, A.; Prasad, A. K.; Raj, H. G.; Parmar, V. S.; Ghosh, B., *Bioorg. Med. Chem.* **2005**, *13*, 1605.
98. Levai, A.; Jeko, J., *J. Heterocycl. Chem.* **2005**, *42*, 739.
99. Yang, Z.-Y.; Xia, Y.; Xia, P.; Cosentino, L. M.; Lee, K.-H., *Bioorg Med. Chem. Lett.* **1998**, *8*, 1483.
100. (a) Bringmann, G.; Schöner, B.; Schupp, O.; Schenk, W. A.; Reuther, I.; Peters, K.; Peters, E.-M.; von Schnering, H. G., *J. Organomet. Chem.* **1994**, *472*, 275. (b) Peters, K.; Peters, E.-M.; Bringmann, G.; Schupp, O., *Z. Naturforsch.* **1996**, *51b*, 431. (c) Bringmann, G.; Wuzik, A.; Schupp, O.; Peters, K.; Peters, E.-M., *Z. Naturforsch* **1997**, *52b*, 355.
101. Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Reddy, K. B.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A., *J. Am. Chem. Soc.* **1995**, *117*, 10227 and references therein.
102. Clyne, D. S.; Weiler, L., *Tetrahedron* **1999**, *55*, 13659.
103. Brunner, A.; Kühnle, F. N. M.; Seebach, D., *Helv. Chim. Acta* **1996**, *79*, 319.
104. Takaguchi, Y.; Furukawa, N., *Chem. Lett.* **1996**, 859.
105. Oh, H. K.; Kim, S. K.; Cho, I. H.; Lee, H. W.; Lee, I., *J. Chem. Soc., Perkin Trans. 2* **2000**, 2306.
106. Kanagasabapathy, S.; Sudalai, A.; Benicewicz, B. C., *Tetrahedron Lett.* **2001**, *42*, 3791.
107. Josse, O.; Labar, D.; Marchand-Brynaert, J., *Synthesis* **1999**, 404.
108. Kurihara, H.; Kobayashi, A.; Kumamoto, T., *Nippon Kagaku Kaishi* **1996**, 875., *Chem. Abstr.* **1996**, *125*, 328420.
109. Stanetty, P.; Kremslehner, M.; Völlenkle, H., *J. Chem. Soc., Perkin Trans. 1* **1998**, 853.
110. Klimenko, S. K.; Trushina, E. V.; Sorokin, N. N.; Yaskeirch, N. N.; Bel'skii, V. K., *Zh. Org. Khim.* **1994**, *30*, 355., *Chem. Abstr.* **1995**, *122*, 132917.
111. Nishio, T.; Sekiguchi, H., *Tetrahedron* **1999**, *55*, 5017.
112. Aimar, M. L.; Kreiker, J.; de Rossi, R. H., *Tetrahedron Lett.* **2002**, *43*, 1947.
113. Gompper, R.; Knieler, R.; Polborn, K., *Z. Naturforsch.* **1993**, *48b*, 1621.
114. (a) Huang, T.-B.; Zhang, J.; Zhu, D.; Yao, W.; Qian, X., *Synthesis* **1999**, 1109. (b) Huang, T.-B.; Quin, X.; Tao, Z.-F.; Wang, K.; Song, G.-H.; Liu, L. F., *Heteroatom. Chem.* **1999**, *10*, 141.
115. Dell, C. P. In *Comprehensive Organic Functional Group Transformations*; Katrizky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Vol. 5, Pergamon: Oxford, 1995, 565, esp. 570f.
116. Murai, T., *Top. Curr. Chem.* **2005**, *251*, 248.
117. Olsson, R.; Hansen, H. C.; Andersson, C.-M., *Tetrahedron Lett.* **2000**, *41*, 7947.
118. Xia, M., *Jingxi Huagong* **1999**, *16*, 34., *Chem. Abstr.* **1999**, *133*, 45136.
119. Langgård, M.; Sandström, J., *J. Chem., Soc. Perkin Trans. 2* **1996**, 435.
120. Feldman, K. S.; Schildknegt, K., *J. Org. Chem.* **1994**, *59*, 1129. A corresponding thionoester *O*-ethyl 2,2-dichloro-3-methylcyclopropanethioate has been obtained by using 2,4-diphenyl-1,3,2,4-dithiadiphosphetane disulfide (Yokoyama, M.; Hasegawa, Y.; Hatanaka, H.; Kawazoe, Y.; Imamoto, T., *Synthesis* **1984**, 827) instead of LR.
121. He, L.-N.; Huang, T.-B.; Cai, F.; Chen, R.-Y., *Phosphorus Sulfur Silicon* **1998**, *132*, 147.

122. Martín-Cantalejo, Y.; Sáez, B.; Soto, J.; Villa, M. J.; Braña, M. F., *Synthesis* **2003**, 2211.
123. Jang, Y.; Bartsch, R. A., *J. Heterocycl. Chem.* **1995**, *32*, 1441.
124. (a) No, K.; Lee, J. H.; Yang, S. H.; Yu, S. H.; Cho, M. H.; Kim, M. J.; Kim, J. S., *J. Org. Chem.* **2002**, *67*, 3165. (b)A related calix[4]arene bis-thioamide has been obtained: Drew, M. G. B.; Beer, P. D.; Ogden, M. I., *Acta Crystallogr. Crystal Struct. Commun.* **1997**, *C53*, 472.
125. Sakamoto, M.; Ishida, T.; Fujita, T.; Watanabe, S., *J. Org. Chem.* **1992**, *57*, 2419.
126. Nishio, T., *J. Org. Chem.* **1997**, *62*, 1106.
127. Kodama, Y.; Ori, M.; Nishio, T., *Helv. Chim. Acta* **2005**, *88*, 187.
128. Sanderson, J. M.; Singh, P.; Fishwick, C. W. G.; Findlay, J. B. C., *J. Chem. Soc., Perkin Trans. 1* **2000**, 3223.
129. Blagbrough, I. S.; Moya, E., *Tetrahedron Lett.* **1994**, *35*, 2057.
130. Ori, M.; Nishio, T., *Heterocycles* **2000**, *52*, 111.
131. Nishio, T., *Tetrahedron Lett.* **1995**, *36*, 6113.
132. Nishio, T.; Konno, Y.; Ori, M.; Sakamoto, M., *Eur. J. Org. Chem.* **2001**, 3553.
133. Nishio, T.; Ori, M., *Helv. Chim. Acta* **2001**, *84*, 2347.
134. Nishio, T., *Helv. Chim. Acta* **1998**, *81*, 1207.
135. Sun, D.; Fang, D.; Lu, Z., *Chin. Chem. Lett.* **1992**, *3*, 415., *Chem. Abstr.* **1992**, *117*, 191423.
136. Arévalo, M. J.; Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Jiménez, J. L.; Palacios, J. C., *Tetrahedron: Asymmetry* **2000**, *11*, 1985.
137. Hoos, R.; Naughton, A. B.; Thiel, W.; Vasella, A.; Weber, W., *Helv. Chim. Acta* **1993**, *76*, 2666.
138. Tran, T. T.; Burgess, A. W.; Treutlein, H.; Perich, J., *J. Peptide Res.* **2001**, *58*, 67.
139. Abo-Ghalia, M. H.; Shalaby, A. M.; El-Eraqi, W. I.; Awas, H. M., *Amino Acids* **1999**, *16*, 425., *Chem. Abstr.* **1999**, *131*, 110914.
140. Aguirre, G.; Cerecetto, H.; Di Maio, R.; González, M.; Porcal, W.; Seoane, G.; Ortega, M. A.; Aldana, I.; Monge, A.; Denicola, A., *Arch. Pharm.* **2002**, *335*, 15.
141. Krinková, J.; Dolezal, M.; Hartl, J.; Buchta, V.; Pour, M., *Farmaco* **2002**, *57*, 71., *Chem. Abstr.* **2002**, *137*, 152209.
142. Reitz, A. B.; Baxter, E. W.; Codd, E. E.; Davis, C. B.; Jordan, A. D.; Maryanoff, B. E.; Maryanoff, C. A.; McDowell, M. E.; Powell, E. T.; Renzi, M. J.; Schott, M. R.; Scott, M. K.; Shank, R. P.; Vaught, J. L., *J. Med. Chem.* **1998**, *41*, 1997.
143. Nieschalk, J.; Schaumann, E., *Liebigs Ann. Chem.* **1996**, 141.
144. Méndez, L.; Delpiccolo, C. M. L.; Mata, E. G., *Synlett* **2005**, 1563.
145. Rajendran, V.; Saxena, A.; Doctor, B. P.; Kozikowski, A. P., *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1521.
146. Imming, P.; Klaperski, P.; Stubbs, M. T.; Seitz, G.; Gundisch, D., *Eur. J. Med Chem.* **2001**, *36*, 375.
147. Grisenti, P.; Magni, A.; Manzocchi, A.; Ferraboschi, P., *Steroids* **1997**, *62*, 504.
148. Lee, B. H.; Han, F., *Tetrahedron Lett.* **1994**, *35*, 1135.
149. Cook, G. R.; Beholz, L. G.; Stille, J. R., *Tetrahedron Lett.* **1994**, *35*, 1669.
150. Budzowski, A.; Linden, A.; Heimgartner, H., *Heterocycles* **2004**, *64*, 417.
151. Polońsky, T., *Tetrahedron: Asymmetry* **1994**, *5*, 149.
152. (a) Igarashi, Y.; Watanabe, N.; Fujita, T.; Sakamoto, M.; Watanabe, S., *Nippon Kagaku Kaishi* **1993**, 1167., *Chem. Abstr.* **1994**, *120*, 289409. (b) Tamaru, Y.; Harayama, H.; Sakata, H.; Konishi, H.; Fugami, K.; Kimura, M.; Tanaka, S.; Okajima, T.; Fukazawa, Y., *Liebigs Ann./Recueil* **1997**, 907.
153. Ostrowska, K.; Żankowska-Jasińska, W.; Ciechanowicz-Rutkowska, M.; Pilati, T., *J. Chem. Res.* **1996**, *(S) 236, (M)* 1352.
154. Qian, X.; Huang, T.-B.; Wei, D.-Z.; Zhu, D.-H.; Fan, M.-C.; Yao, W., *J. Chem. Soc., Perkin Trans. 2* **2000**, 715.
155. Jarecka, D.; Besch, A.; Otto, H.-H., *Monatsh. Chem.* **2003**, *134*, 901.
156. Bakulev, V. A.; Berseneva, V. S.; Belskaia, N. P.; Morzherin, Y. Y., *Org. Biomol. Chem.* **2003**, *1*, 134.
157. Takechi, H.; Machida, M., *Chem. Pharm. Bull.* **1997**, *45*, 1.
158. Zhu, X.; Giordano, T.; Yu, Q.-S.; Holloway, H. W.; Perry, T. A.; Lahiri, D. K.; Brossi, A.; Greig, N. H., *J. Med. Chem.* **2003**, *46*, 5222.
159. Rico-Gomez, R.; Najera, F.; Lopez-Romero, J. M.; Canada-Rudner, P., *Heterocycles* **2000**, *53*, 2275.
160. Peyrane, F.; Fourrey, J.-L.; Clivio, P., *Chem. Commun.* **2003**, 736.
161. Felczak, K.; Bretner, M.; Kalikowski, T.; Shugar, D., *Nucleosides Nucleotides* **1993**, *12*, 245.
162. Fossey, C.; Landelle, H.; Lasuree, D.; Robba, M., *Nucleosides Nucleotides* **1993**, *12*, 973.
163. Leydier, C.; Bellon, L.; Barascut, J.-L.; Deydier, J.; Maury, G.; Pelicano, H.; El Alaoui, M. A.; Imbach, J.-L., *Nucleosides Nucleotides* **1994**, *13*, 2035.
164. Voss, J.; Wirsching, J.; Schulze, O.; Adiwidjaja, G.; Giesler, A.; Balzarini, J.; De Clerq, E., *Nucleosides Nucleotides* **2004**, *23*, 1609.
165. Wojczewski, C.; Schwarzer, K.; Engels, J. W., *Helv. Chim. Acta* **2000**, *83*, 1268.
166. Ju, J.; McKenna, C. E., *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1643.
167. Shimomura, N.; Matsutani, T.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3100.
168. Cow, C. C.; Harrison, P. H., *J. Org. Chem.* **1997**, *62*, 8834.
169. Przychodzeń, W.; Chimiak, A., *Phosphorus Sulfur Silicon* **1998**, *143*, 77.
170. Hoeg-Jensen, T., *Phosphorus Sulfur Silicon* **1996**, *108*, 257.
171. (a) Morita, H.; Nagashima, S.; Takeya, K.; Itokawa, H., *J. Chem. Soc. Perkin Trans. 1* **1995**, 2327. (b) Morita, H.; Nagashima, S.; Takeya, K.; Itokawa, H., *Bioorg. Med. Chem. Lett.* **1995**, *5*, 677.
172. Morita, H.; Yun, Y. S.; Takeya, K.; Itokawa, H.; Shirota, O., *Bioorg. Med. Chem.* **1997**, *5*, 631.
173. Sifferlen, T.; Rueping, M.; Gademann, K.; Jaun, B.; Seebach, D., *Helv. Chim. Acta* **1999**, *82*, 2067.
174. (a) Hitosuyanagi, Y.; Matsumoto, Y.; Sasaki, S.-I.; Yamaguchi, K.; Itokawa, H.; Takeya, K., *Tetrahedron Lett.* **2001**, *42*, 1535. (b) Hitosuyanagi, Y.; Sasaki, S.-I.; Matsumoto, Y.; Yamaguchi, K.; Itokawa, H.; Takeya, K., *J. Am. Chem. Soc.* **2003**, *125*, 7284.
175. Altamura, M.; Balacco, G.; Giolitti, A.; Guidi, A.; Patacchini, R.; Renzetti, A. R.; Triolo, A.; Maggi, C. A., *Lett. Drug Design Discov.* **2004**, *1*, 285., *Chem. Abstr.* **2004**, *142*, 114422.
176. Lei, Y.; Shi, J.; Yu, M.; Zheng, X., *Acta Crystallogr. Struct. Rep. Online* **2005**, *E61*, o873.
177. Raghavan, S.; Anuradha, K., *Synlett* **2003**, 711.
178. Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Gupta, M. K., *Tetrahedron Lett.* **2004**, *45*, 5873.
179. Raposo, M. M. M.; Kirsch, G., *Heterocycles* **2001**, *55*, 1487.
180. Ertas, E.; Ozturk, T., *Tetrahedron Lett.* **2004**, *45*, 3405.
181. Mehta, G.; Gagliardini, V.; Schaefer, G.; Gleiter, R., *Tetrahedron Lett.* **2003**, *44*, 9313.
182. Okuma, K.; Shigetomi, T.; Shibata, S.; Shioji, K., *Bull. Chem. Soc. Jpn.* **2004**, *77*, 187.
183. Huang, H.-M.; Yu, H.-T.; Chen, P.-L.; Han, J.; Meng, J.-B., *Youji Huaxue* **2004**, *24*, 502., *Chem. Abstr.* **2004**, *141*, 295952.
184. Rafiqul, I. M.; Shimada, K.; Aoyagi, S.; Fujisawa, Y.; Takikawa, Y., *Heteroatom. Chem.* **2004**, *15*, 208.
185. Dodd, D. S.; Martinez, R. L., *Tetrahedron Lett.* **2004**, *45*, 4265.
186. Deng, S.-L.; Chen, R.-Y., *Phosphorus Sulfur Silicon* **2003**, *178*, 211.
187. Moustafa, H. M., *Phosphorus Sulfur Silicon* **2003**, *178*, 1397.
188. Mosbah, M. B.; Rekik, A.; Kossentini, M.; Salem, M., *Compt. Rend. Chim.* **2003**, *6*, 445.
189. Mohamed, N. R.; El-Saidi, M. M. T.; Hassaneen, H. M.; Erian, A. W., *Phosphorus Sulfur Silicon* **2004**, *179*, 521.

190. Abdel-Malek, H. A., *Heterocycl. Commun.* **2003**, *9*, 457.
191. Abd Allah, O. A., *Phosphorus Sulfur Silicon* **2003**, *178*, 1115.
192. Mohamed, N. R.; El-Saidi, M. M. T.; Abdallah, T. A.; Nada, A. A., *Phosphorus Sulfur Silicon* **2004**, *179*, 2387.
193. Deng, D.-L.; Chen, R.-Y., *Monatsh. Chem.* **2004**, *135*, 1113.
194. Oshida, H.; Ishii, A.; Nakayama, J., *Tetrahedron Lett.* **2004**, *45*, 1331.
195. Mosbah, M. B.; Chouaib, H.; Kossentini, M.; Salem, M., *Phosphorus Sulfur Silicon* **2003**, *178*, 1433.
196. Przychodzeń, W., *Phosphorus Sulfur Silicon* **2004**, *179*, 1621.
197. He, L.; Luo, Y.; Li, K.; Yang, G.; Ding, M.; Liu, X.; Wu, T., *Phosphorus Sulfur Silicon* **2002**, *177*, 2675.
198. Tongcharoensirikul, P.; Suarez, A.; Voelker, T.; Thompson, C. M., *J. Org. Chem.* **2004**, *69*, 2322.
199. Wu, X.; Mahalingam, A. K.; Alterman, M., *Tetrahedron Lett.* **2005**, *46*, 1501.
200. Ono, Y.; Sugihara, Y.; Ishii, A.; Nakayama, J., *J. Am. Chem. Soc.* **2003**, *125*, 12114.
201. Nair, S. K.; Jose, A. M.; Asokan, C. V., *Synthesis* **2005**, 1261.

2,3-Bis[(4-methylphenyl)thio]-1,3,2,4-dithiadiphosphetane 2,4-Disulfide



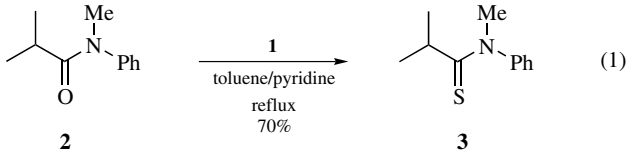
1

[114234-09-2] $C_{14}H_{14}P_2S_6$ (MW 436.60)
InChI = 1/C14H14P2S6/c1-11-3-7-13(8-4-11)19-15(17)21-16(18,22-15)20-14-9-5-12(2)6-10-14/h3-10H,1-2H3
InChIKey = WMYQGZHFMUDZIS-UHFFFAOYAS

(reagent used for the thionation of amides and lactams[1])

Alternate Names: 2,4-bis[(4-methylphenyl)thio]-1,3,2,4-dithiadiphosphetane-2,4-disulfide; 2,4-bis[(4-methylphenyl)thio]-1,3,2λ^5,4λ^5-dithiadiphosphetane-2,4-dithione; Davy-reagent *p*-tolyl.
Physical Data: mp 209–213 °C (dec).
Solubility: soluble in pyridine, toluene, dioxane, and THF.
Form Supplied in: pale yellow crystals/solid; purum, >97.0%.
Preparative Methods: can be prepared by the reaction of P_4S_{10} (0.3 mol) and 4-methylthiophenol (thio-*p*-cresol; 1.0 mol) in toluene (500 ml), with 4 h at reflux temperature.
Purity: recrystallization from toluene.

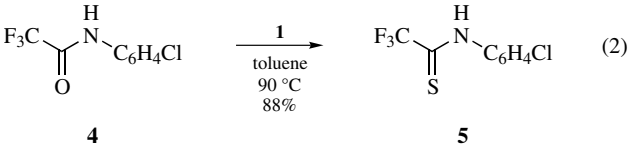
Thionation of Amides. 2,4-Bis[(4-methylphenyl)thio]-1,3,2,4-dithiadiphosphetane-2,4-disulfide (**1**) reacts with carboxamides to give the corresponding thioamides. Usually, this thionation reaction is performed in a 1:1 mixture of toluene and pyridine at 70–110 °C. For example, the treatment of *N*,2-dimethyl-*N*-phenylpropanamide (**2**) with **1** in toluene/pyridine under reflux for ca. 15 h leads to thioamide **3** in 70% yield (eq 1).[1] After only 3 h, 70% of the starting material (**2**) is consumed and **3** is obtained in 66% yield.



2 **3** (1)

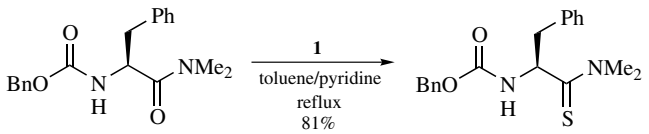
The thionation of carboxamides with **1** shows some remarkable selectivities:[1] the reagent is especially suited for the formation of *N*,*N*-disubstituted thiocarboxamides. Under similar conditions as described above, the transformations of 2-methyl-*N*-phenylpropanamide and benzamide gave the corresponding thioamides in only 27% and 4.5% yields, respectively. This selectivity is somehow complementary compared with that of Lawesson's reagent.

The thionation of trichloroacetamides with Lawesson's reagent fails, whereas the corresponding *N*-aryl and *N*-benzylthioacetamides are obtained in good yield on treatment with **1** in toluene.[2] For example, *N*-methyl-*N*-phenyltrichlorothioacetamide and *N*-(4-chlorophenyl)trifluorothioacetamide (**5**) have been prepared in 78% and 88% yields, respectively (eq 2).



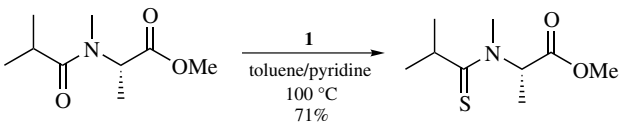
4 **5** (2)

Thionation of Cbz-protected α-amino acid dimethylamides of type **6** proceeds smoothly under the standard conditions to give selectively Cbz-protected α-amino acid thioamides **7** (eq 3),[1] i.e., thionation of carboxamides is preferred to that of carbamates.



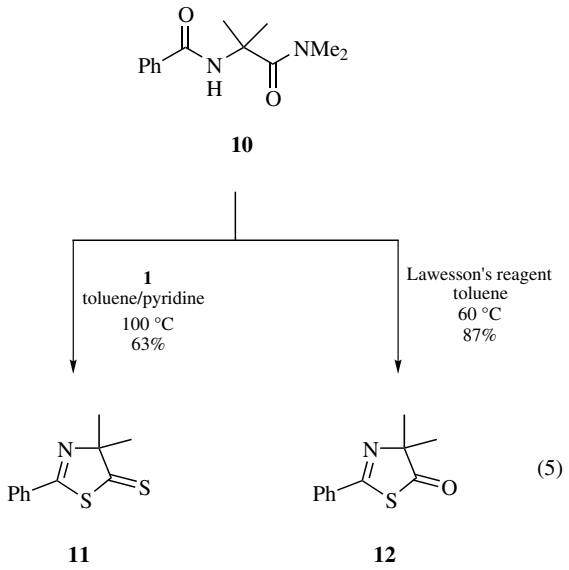
6 **7** (3)

A similar selectivity is observed with respect to carboxamides and carboxylic esters; thionation of *N*-acylated α-amino acid esters of type **8** with **1** leads to thioamides **9** exclusively (eq 4).[3]



8 **9** (4)

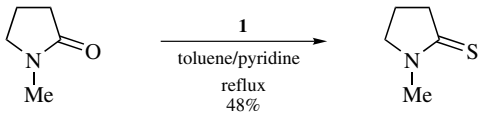
Synthesis of 1,3-Thiazole-5(4*H*)-thiones. The preferential thionation of *N*,*N*-disubstituted carboxamides can be used for a convenient synthesis of 2,4,4-trisubstituted 1,3-thiazole-5(4*H*)-thiones of type **11**. Treatment of *N*-acylated α,α-disubstituted α-amino acid amide **10** with **1** in toluene/pyridine at 100 °C gives **11** as the sole product.[1] In contrast, the analogous reaction with Lawesson's reagent leads exclusively to the corresponding 1,3-thiazol-5(4*H*)-one **12** (eq 5).[1,4–6]



This difference can be rationalized by a reverse sequence of thionation of the diamide and the assumption that the analogs of **10** with a thiobenzoyl group undergo a spontaneous cyclization via elimination of dimethylamine to give 1,3-thiazole derivatives.

1,3-Thiazole-5(4*H*)-thiones of type **11** are also obtained by the thionation of *N*-acylated α,α-disubstituted α-amino acid thioamides with **1**.[1] In this case, the reaction with Lawesson's reagent parallels that with **1**.

Thionation of Lactams. The thionation of *N*-substituted lactams with **1** in toluene/pyridine provides the corresponding thiolactams, e.g., *N*-methylpyrrolidin-2-one (**13**) is transformed into *N*-methylpyrrolidine-2-thione (**14**) (eq 6).[1] The observed selectivity in the case of lactams is similar to that of amides; the reaction of *N*-unsubstituted lactams with **1** is sluggish, i.e., the product pyrrolidine-2-thione is formed in very low yield.



Recently, thionation of an antitumor cyclic hexapeptide containing three -CO-NH- and three -CO-NMe- lactam groups has been studied.[7] The thionation with Lawesson's reagent occurs with high selectivity at the -CO-NH- group of Tyr-3 and only very small amounts of the product of dithionation at -CO-NH- of Tyr-3 and Tyr-6 are formed, whereas the reaction with **1** in dioxane yields two monothio and three dithio derivatives. The two main products are the same as obtained in the reaction with Lawesson's reagent, but their ratio is remarkably different. One of the minor dithionated products contains a -CS-NMe- group of Ala-2.

Related Reagents. 1,3,2,4-Dithiadiphosphetane, 2,4-Bis-(methylthio)-2,4-disulfide (Davy-reagent methyl);[8–10] 1,3,2,4-dithiadiphosphetane, 2,4-Bis(ethylthio)-2,4-disulfide (Davy-reagent ethyl);[8,9] 1,3,2,4-Dithiadiphosphetane, 2,4-Bis(phenylthio)-2,4-disulfide;[11] 1,3,2,4-Dithiadiphosphetane, 2,4-Bis-[(4-methoxyphenyl)thio]-2,4-disulfide;[8] 1,3,2,4-Dithiadiphosphetane, 2,4-bis(4-methoxyphenyl)-2,4-disulfide (Lawesson Reagent).[12,13]

1. Wipf, P.; Jenny, C.; Heimgartner, H., *Helv. Chim. Acta* **1987**, *70*, 1001.
2. Braverman, S.; Cherkinsky, M.; Kedrova, L., *Tetrahedron Lett.* **1998**, *39*, 9259.
3. Breitenmoser, R. A.; Heimgartner, H., *Helv. Chim. Acta* **2002**, *85*, 885.
4. Obrecht, D.; Heimgartner, H., *Chimia* **1982**, *36*, 78.
5. Obrecht, D.; Prewo, R.; Bieri, J. H.; Heimgartner, H., *Helv. Chim. Acta* **1982**, *65*, 1825.
6. Jenny, C.; Heimgartner, H., *Helv. Chim. Acta* **1986**, *69*, 374.
7. Hitotsuyanagi, Y.; Matsumoto, Y.; Sasaki, S.; Suzuki, J.; Takeya, K.; Yamaguchi, K.; Itokawa, H., *J. Chem. Soc., Perkin Trans. 1* **1996**, 1749.
8. Davy, H., *J. Chem. Soc., Chem. Commun.* **1982**, 457.
9. Davy, H.; Metzner, P., *J. Chem. Res. (S)* **1985**, 272.
10. Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S. O., *Tetrahedron* **1984**, *40*, 2047.
11. Yokoyama, M.; Hasegawa, Y.; Hatanaka, H.; Kawazoe, Y.; Imamoto, T., *Synthesis* **1984**, 827.
12. Cherkasov, R. A.; Kutyrev, G. A.; Pudovik, A. N., *Tetrahedron* **1985**, *41*, 2567.
13. Cava, M. P.; Levinson, M. J., *Tetrahedron* **1985**, *41*, 5061.

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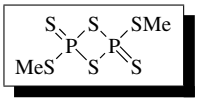
2,4-Bis(methylthio)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide



[82737-61-9] $C_2H_6P_2S_6$ (MW 284.38)
InChI = 1/C2H6P2S6/c1-7-3(5)9-4(6,8-2)10-3/h1-2H3
InChIKey = OIEQWZXDRGOGHA-UHFFFAOYAG

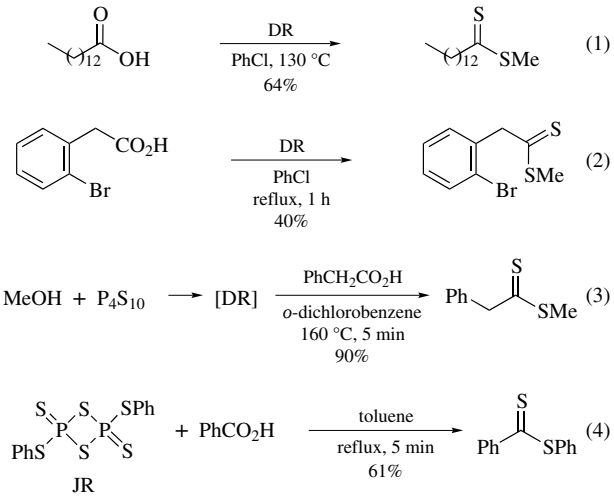
(reagent for the conversion of carboxylic acids into dithioesters and carbonyl groups into thiocarbonyl groups)

Alternate Name: Davy's reagent.
Physical Data: mp 125–136 °C.
Solubility: sol hot aromatic hydrocarbons, chlorobenzene.
Form Supplied in: pale yellow, evil-smelling crystals.
Analysis of Reagent Purity: ^{1}H NMR spectrum: δ = 2.86 (d, J = 20 Hz, CH_3).
Preparative Method: reaction of P_4S_{10} with methanethiol or methanol.[1]
Purification: washing with cyclohexane.
Handling, Storage, and Precautions: should be stored in the cold with exclusion of moisture. It is very toxic and must be handled under a hood or in glove-boxes due to its intolerable odor and the hazardous methanethiol which is easily liberated with moisture.

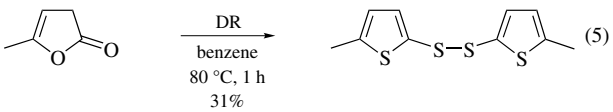
Introduction. 2,4-Bis(methylthio)-1,3,2,4-dithiadiphosphetane 2,4-disulfide as well as the analogous ethylthio, isopropylthio, and benzylthio derivatives have been introduced as reagents for syntheses by Davy and Metzner. These compounds (Davy's reagent, DR) can be used in the same way as Lawesson's reagent,

LR, for the thionation of carbonyl groups. DR is, however, considerably more reactive and in many cases more selective than LR. Furthermore, it exhibits the unique ability to transform carboxylic acids into dithiocarboxylic esters in one step. Similar dithiadiphosphetane disulfides with arylthio substituents have been designed in order to achieve an even improved effectiveness in thionation reactions and also to produce a more conveniently handled reagent compared with the obnoxious DR. The so-called Japanese reagent (JR), 2,4-bis(phenylthio)-1,3,2,4-dithiadiphosphetane 2,4-disulfide,[3] has recently found considerable synthetic application.

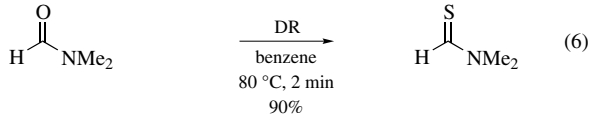
Transformation of Carboxylic Acids into Dithiocarboxylic Esters.[2,4] Dithioesters bearing functional groups such as C=C double bonds,[2] halogen,[2,5] nitro,[6] or phenoxy groups[2] are obtained with yields of up to 68% on reaction of aliphatic (eq 1)[2b] or aromatic (eq 2)[5b] carboxylic acids with DR in boiling chlorobenzene. Acid chlorides can also be used as starting material.[2b,4] Isolation and handling of pure DR can be avoided by using a one-pot procedure (eq 3),[7] which consists of first reacting methanol or ethanol with P_4S_{10} followed by addition of the carboxylic acid and further P_4S_{10}. The above mentioned JR enables one to prepare phenyl dithiocarboxylates in extremely short reaction times (eq 4).[3]



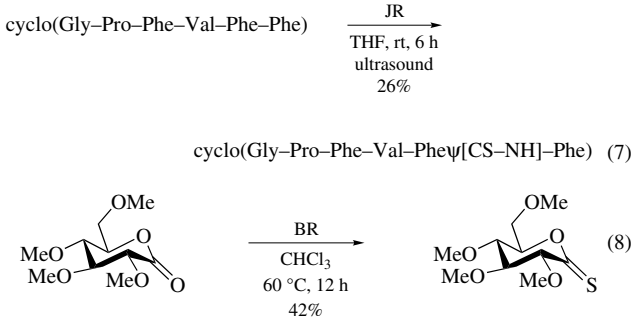
Thionation of Carbonyl Compounds. Diaryl thioketones[8] and 2,4-bis(diphenylmethylene)cyclobutane-1,3-dithione[9] were obtained on reaction of the corresponding ketones with DR. On the other hand, JR was utilized to thionate selectively the carbonyl group of benzil monophenylimine.[10] If carboxylic esters or lactones are reacted with DR, dithiocarboxylic esters[4] or dithiolactones[4,8] are formed, i.e. the carbonyl group is thionated and the alkoxy group is substituted by an alkylthio group. Bis(5-methyl-2-thienyl) disulfide is produced in this way from a butenolide (eq 5).[4]



A systematic study on the thionation reactions of primary, secondary, and tertiary amides and lactams with DR compared with LR and 2,4-bis(4-phenoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, the so-called Belleau's reagent (BR),[11] has been performed.[12] Generally, good yields are obtained with whichever reagent is used, but each reagent may exhibit advantages in a special case. DR has been mainly utilized for the preparation of simple thioamides (eq 6).[8]



JR has found application in endothiopeptide synthesis.[3–14] One carbonyl group of a cyclohexapeptide is selectively thionated with JR (eq 7).[15] The cyclic thiopeptide exhibits enhanced effectiveness as an inhibitor of triosephosphate isomerase (TIM). This results from the pronounced alteration of the backbone conformation which is due to different hydrogen bridges. Belleau's reagent, BR, can be used similarly to JR to prepare thiooligopeptides selectively[16,17] or thiono esters of the carbohydrate series (eq 8).[18]



1. Davy, H., *Sulfur Lett.* **1985**, *3*, 39.
2. (a) Davy, H., *J. Chem. Soc., Chem. Commun.* **1982**, 457. (b) Davy, H.; Metzner, P., *J. Chem. Res. (S)* **1985**, 272; *J. Chem. Res. (M)* **1985**, 2701.
3. Yokoyama, M.; Hasegawa, Y.; Hatanaka, H.; Kawazoe, Y.; Imamoto, T., *Synthesis* **1984**, 827.
4. Yousif, N. M.; Pedersen, U.; Yde, B.; Lawesson, S.-O., *Tetrahedron* **1984**, *40*, 2663.
5. (a) Böge, A.; Voss, J., *Chem. Ber.* **1990**, *123*, 1733. (b) Gade, T.; Streek, M.; Voss, J., *Chem. Ber.* **1992**, *125*, 127.
6. Wollny, B.; Voss, J., *Phosphorus Sulfur Silicon* **1992**, *71*, 231.
7. Davy, H.; Metzner, P., *Chem. Ind. (London)* **1985**, 824.
8. Pedersen, U.; Yde, B.; Yousif, N. M.; Lawesson, S.-O., *Sulfur Lett.* **1983**, *1*, 167.
9. Strehlow, T.; Voss, J.; Spohnholz, R.; Adiwidjaja, G., *Chem. Ber.* **1991**, *124*, 1397.
10. Hafez, T. S., *Phosphorus Sulfur Silicon* **1992**, *66*, 87.
11. Lajoie, G.; Lépine, F.; Maziak, L.; Belleau, E., *Tetrahedron Lett.* **1983**, *24*, 3815.
12. Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S.-O., *Tetrahedron* **1984**, *40*, 2047.
13. Guziec, F. S., Jr.; Wasmund, L. M., *J. Chem. Res. (S)* **1989**, 155; *J. Chem. Res. (M)* **1989**, 1301.
14. Shalaby, A. M.; Shabana, R.; Salem, E. M. S.; Osman, S. A. M., *Egypt. J. Chem.* **1988**, *31*, 697 (*Chem. Abstr.* **1992**, *117*, 131 540h).
15. Kessler, H.; Matter, H.; Geyer, A.; Diehl, H.-J.; Köck, M.; Kurz, G.; Opperdoes, F. R.; Callens, M.; Wierenga, R. K., *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 328.

16. Sauvé, G.; Rao, V. S.; Lajoie, G.; Belleau, B., *Synlett* **1985**, *63*, 3089.
17. Campbell, M. M.; Ross, B. C.; Semple, G., *Tetrahedron Lett.* **1989**, *30*, 1997.
18. Barrett, A. G. M.; Lee, A. C., *J. Org. Chem.* **1992**, *57*, 2818.

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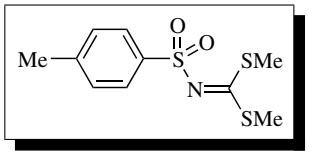
N-[Bis(methylthio)methylene]-*p*-toluenesulfonamide

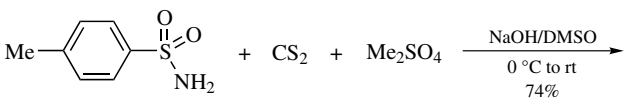


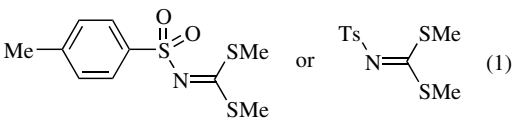
[2651-15-2] $C_{10}H_{13}NO_2S_3$ (MW 275.41)
InChI = 1/C10H13NO2S3/c1-8-4-6-9(7-5-8)16(12,13)11-10(14-2)15-3/h4-7H,1-3H3
InChIKey = OWIPGZGAUSIOAX-UHFFFAOYAS

(the title reagent reacts with a range of different nucleophilic reagents to give medicinally useful guanidinyl derivates and various heterocyclic compounds. In addition, a unique application of this reagent in 1,3-dipolar cycloaddition reactions has been developed)

Physical Data: mp 110–112 °C.

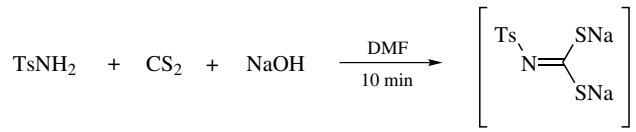
Preparation. *N*-Bis(methylthio)methylene-*para*-methylbenzenesulfonamide (**1**) can be prepared by condensing *para*-toluenesulfonamide with carbon disulfide (CS_2) in an alkaline medium using either DMSO as solvent and dimethylsulfate (Me_2SO_4) as the methylating agent (eq 1),[1] or DMF as solvent and MeI as the methylating agent (eq 2).[2]

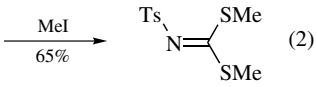




1

A typical procedure involves dissolving 1 mol of *para*-toluenesulfonamide in sufficient DMSO or DMF (~150 mL per 0.2 mol[2]) at room temperature. After adding and dissolving 2 mol of NaOH, 1 mol of carbon disulfide was added carefully at 0 °C over a few minutes. After stirring for another 30 min at 0 °C, 2 mol of Me_2SO_4 was added dropwise over 1 h. After warming up to room temperature, ample water was added and the resulting crystalline precipitate was collected via filtration. The filter cake was washed with water, dried, and recrystallized using MeOH. The temperature needed to be raised to 50–60 °C when using MeI as the alkylating agent.



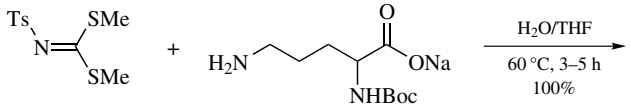


1

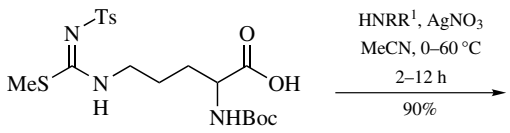
Applications in Organic Synthesis. *N*-Bis(methylthio) methylene-*para*-toluenesulfonamide has been extensively employed as an electrophilic agent for condensation with different nucleophiles such as amines, alcohols, thiols, and anionic species to synthesize medicinally useful guanidinyl derivates and heterocycles.

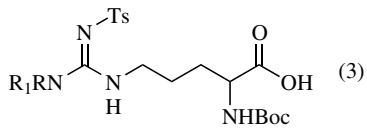
Synthesis of Guanidine Derivatives.

Using Two Different Amines. The sodium salt of *N*-Boc ornithine could be reacted with **1** to give a mono-addition product (eq 3).[3] Subsequent addition of a second amine ($HNRR^1$) allowed the formation of *N*-Boc arginine derivatives in good yields. These derivatives are useful for solid-phase peptide synthesis.



1 ornithine

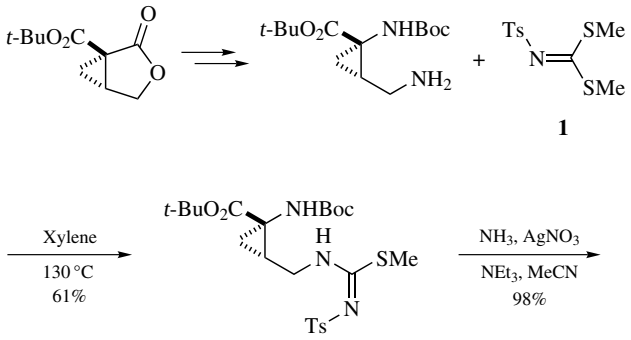


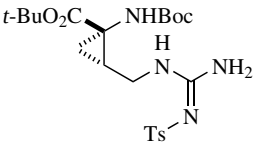


arginines

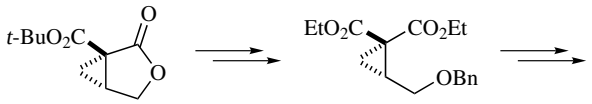
Burgess and co-workers have illustrated the use of reagent **1** in the total syntheses of all four stereoisomers of carnosadine, a cyclopropane amino acid based natural product isolated from red marine alga (eqs 4 and 5).[4,5] These synthetic efforts ultimately led to preparations of a series of novel 2,3-methanologs of

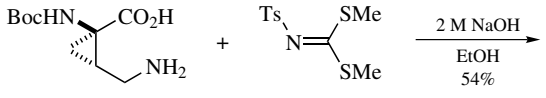
natural amino acids for constructing peptidomimetics with unique conformational motifs and potential medicinal value.

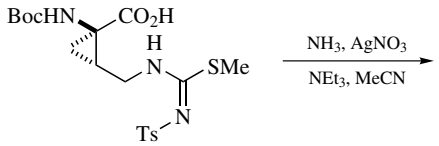


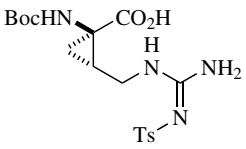


(4)



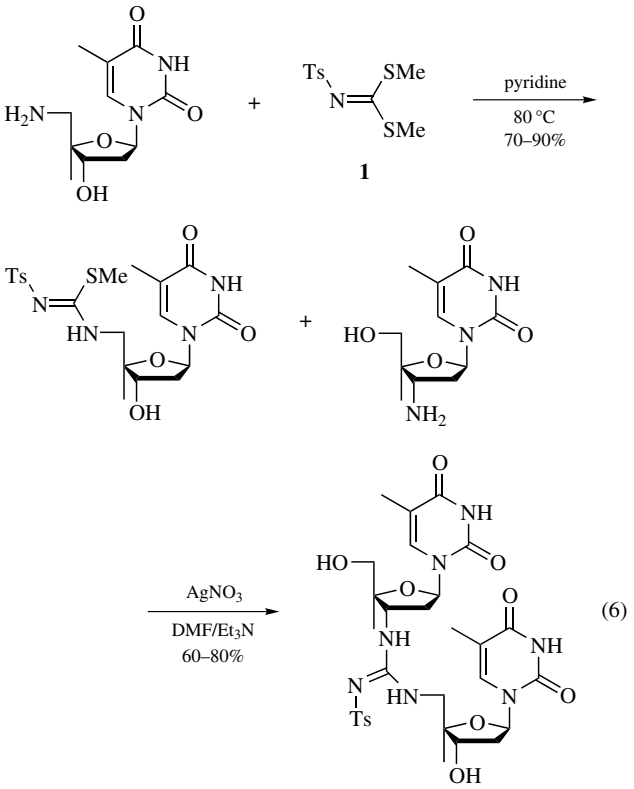




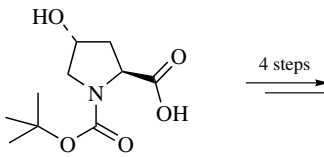


(5)

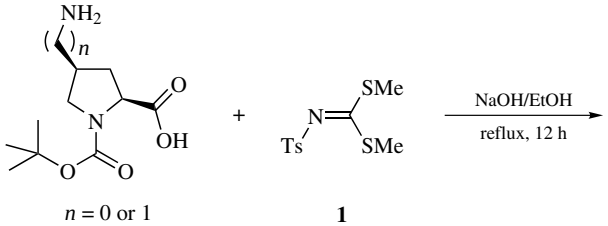
In a related manner, reagent **1** has been used to prepare thymidine dimers that are linked by a guanidine unit (eq 6).[6,7] These dimers were subsequently incorporated into oligothymidylates to study base pairing properties.[6,7] Another example of guanidination of amines is shown in eq 7 for the synthesis of conformationally constrained arginine derivatives starting from 4-hydroxy-prolines.[8] Although only one stereoisomer is shown, all four possible stereoisomers of 4-hydroxy-prolines were employed in this manner.

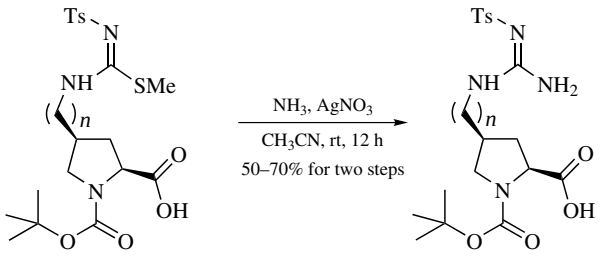


(6)



4-hydroxy-proline

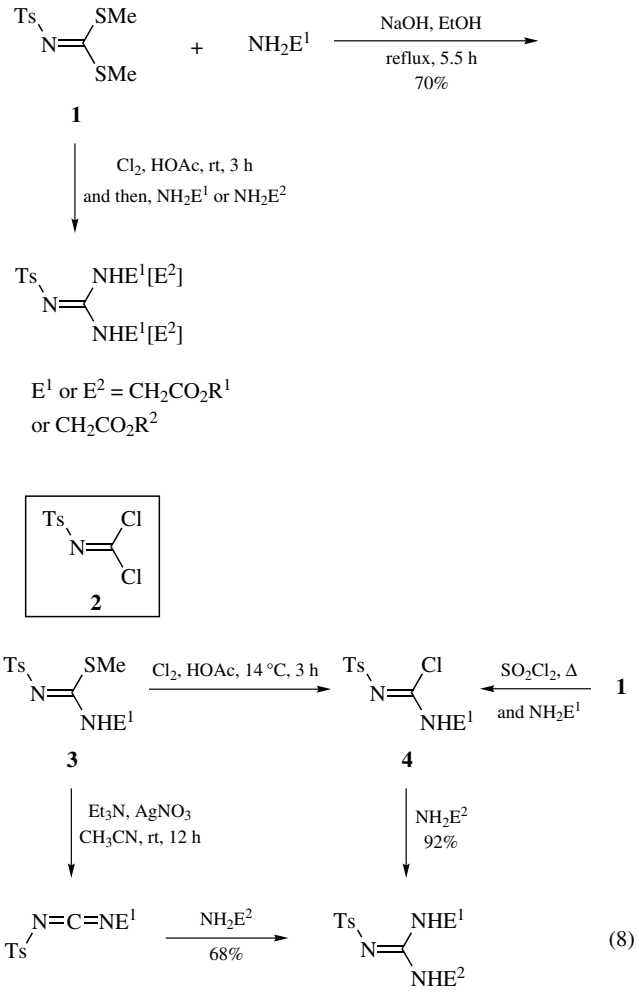




(7)

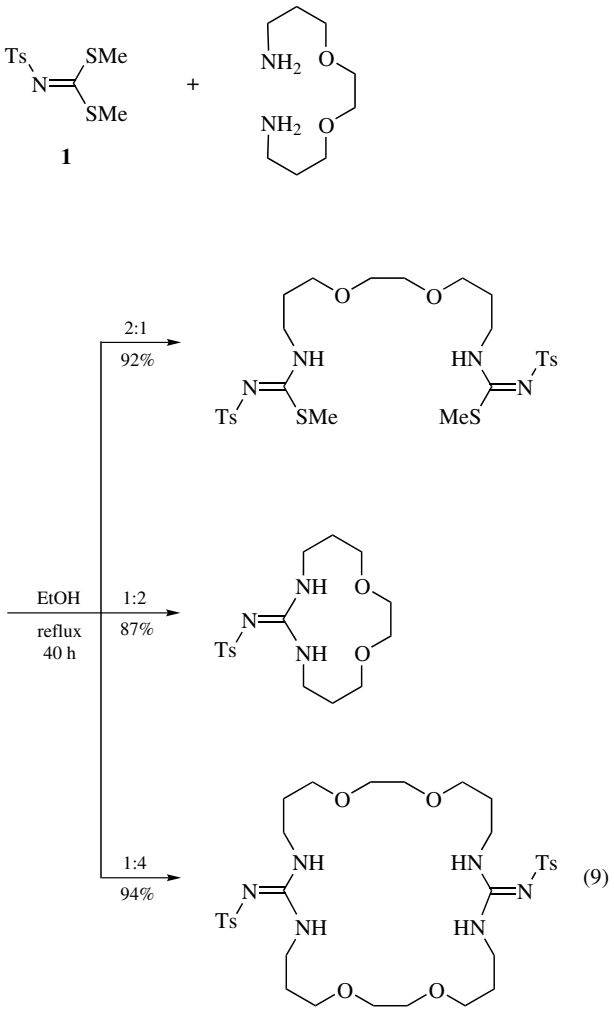
In general, by comparing all the examples shown thus far, unless $AgNO_3$ is used, reactions of amine with **1** require refluxing conditions in solvents such as CH_3CN, H_2O/THF, $CHCl_3$, and alcoholic solvents to displace one of the two methyl sulfide groups.

Some guanidinyl diesters could be prepared using reagent **1**.[9a] As shown in eq 8, symmetric guanidinyl diesters can be derived directly via chlorination of **1** in glacial acetic acid[9b,9c] at rt followed by addition of 2.0 equiv of an amino ester NH_2E^1 (or NH_2E^2) to dichloro imine intermediate **2** at rt. In addition to preparing guanidines via addition of amines, it is noteworthy that dichloroimine **2** has also been employed in various reactions with thiols, thiolates, and alkoxides to give the corresponding imido-dithiocarbamates and imido-carbamates.[9b,9c] Unsymmetric ones can be prepared by first refluxing the sodium salt of the first amino ester NH_2E^1 with reagent **1** to give mono-ester intermediate **3**. Subsequent elimination of HSMe in **3** using $AgNO_3/Et_3N$ followed by addition of a second amino ester NH_2E^2 to the resulting carbodiimide leads to unsymmetric guanidinyl diesters. Alternatively, mono-ester intermediate **3** could be chlorinated carefully using Cl_2 and HOAc at low temperature to give chloro amidate **4** followed by addition of the second amino ester NH_2E^2. Chloro amidate **4** could also be prepared directly from **1** via refluxing with SO_2Cl_2 followed by addition of the first amino ester NH_2E^1.



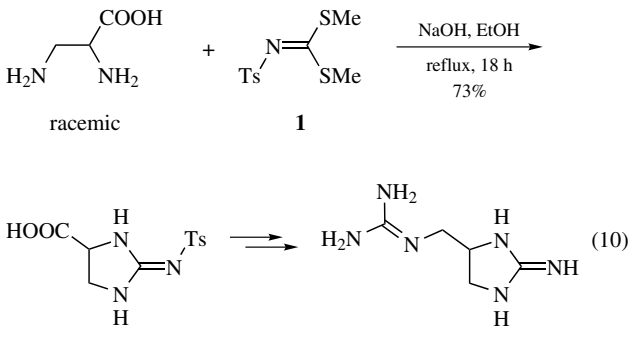
(8)

Using Diamines. Diamines could also be used to construct guanidines employing reagent **1**. As shown in eq 9, depending upon the molar ratio, reactions of **1** with the diamine derived from triethylene glycol led to various different macrocycles potentially useful in host-guest chemistry. [10]



(9)

Reactions of reagent **1** with other simple diamines such as 1,2- (eqs 10 and 11),[11,12] 1,3- (eqs 12 and 13),[13,14] and 1,4-diamines (eqs 14 and 15)[15,16] have all been reported to give interesting cyclic guanidines. Particularly, they have been featured in the synthesis of natural products such as DL-capreomycidine (eq 13),[14] and in Rappoport's bicyclic guanidines with a bridgehead nitrogen atom (eq 14).[15] All these studies were carried out using racemic diamines.



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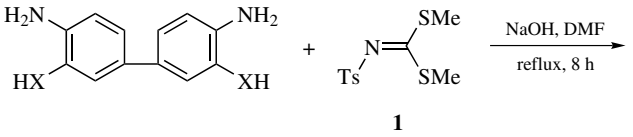

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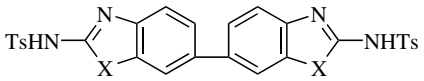
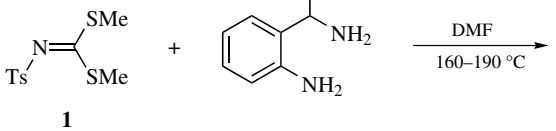


(11)

X	Yield (%)
O	73
S	73
NH	—



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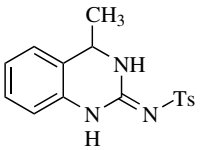

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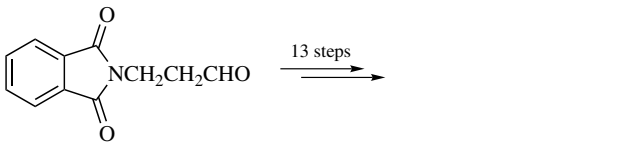

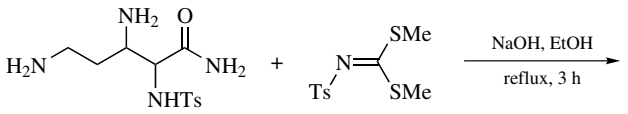

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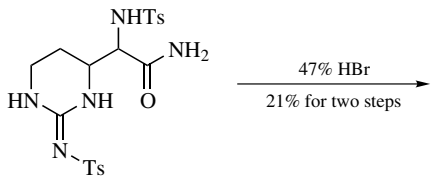

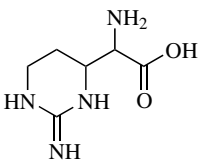

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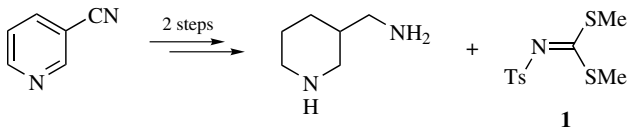

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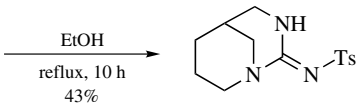

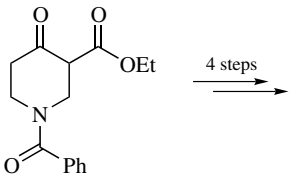

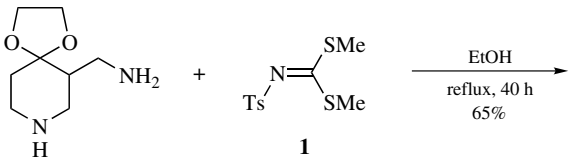

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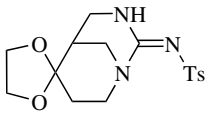

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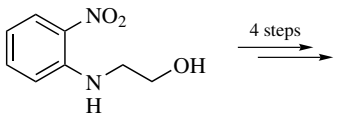

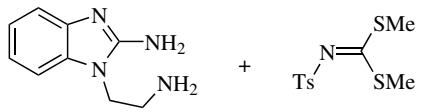

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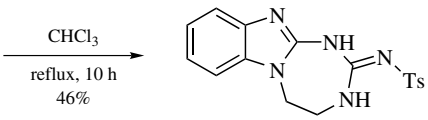
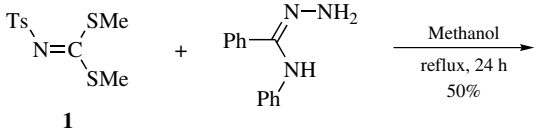
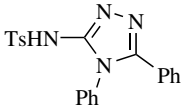


(15)

Synthesis of Triazoles. *N*-Bis(methylthio)methylene-*para*-toluenesulfonamide has been utilized in the synthesis of substituted triazoles that possess antimicrobial activities (eqs 16–18).[17–19] The substituted triazoles in eq 17 were specifically used as precursors for constructing several fused heterocycles that exhibit leishmanicidal activity against *L. donovani*. The level of regioselectivity in these annulation reactions is also noteworthy.





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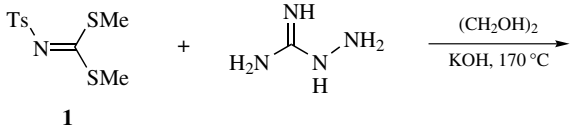
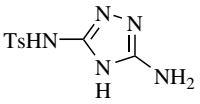




(17)

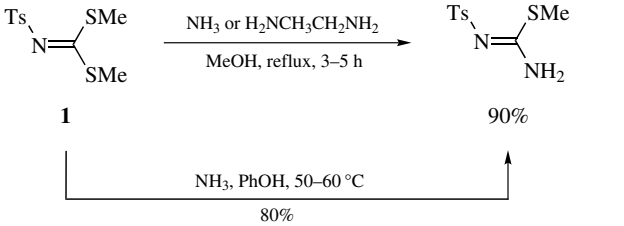
Other Nucleophilic Addition Reactions.

Addition of Neutral Nucleophiles. The previous two sections have already showcased many of the additions of neutral nucelophiles such as amines and alcohols to **1**. The remaining examples, mostly mono-addition of amines, are summarized below.

In Kuwayama and Kataoka's preparations of **1**, the addition of ammonia or ethylene diamine under refluxing conditions in MeOH was also reported.[1] In addition, Gompper also illustrated addition of ammonia to **1** in heated phenol (eq 19).[2]

In addition, a series of acyclic and cyclic amines have been added to reagent **1** in refluxing MeOH to afford compounds that possess promising activities against Gram +ve and Gram −ve bacteria (eq 20).[20]

Rapoport reported preparations of amino guanidines for studies of UV-*p*H profiles. It was found that the addition of a substituted amine must precede the addition of ammonia, otherwise no desired amino guanidines will be found (eq 21).[21] Finally, another example involved addition of the dianion of α-amino acetic acid to reagent **1** (eq 22).[22]



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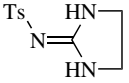


(19)

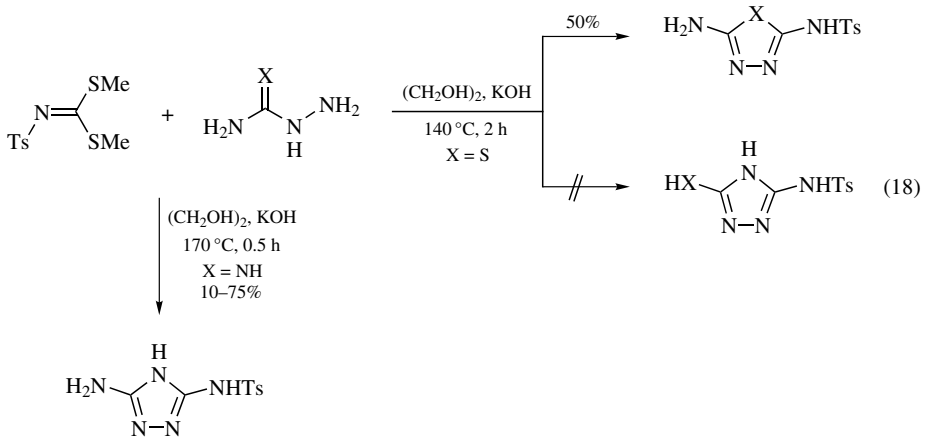
46%

Addition of Ylides. *N*-Bis(methylthio)methylene-*para*-toluenesulfonamide has been added to a series of ylides with some of these reactions leading to heterocyclic compounds in a formal cycloaddition manner. As shown in eq 23, reactions of reagent **1** with the ylide generated by deprotonating the bromide salt of α-pyridinium ethyl acetate led to imidazo[1,2-*a*]pyridines in modest yields presumably via another ylide intermediate **5**.[23a] The product resulting from transfer of the Ts group dominated when the reaction was carried out in refluxing xylene. This process can be considered as a formal [3 + 2] cycloaddition. The same reaction can also provide imidazo [1,2-a]isoquinolines when the bromide salt of α-isoquinolinium ethyl acetate was used.[23b]

Tominaga and Kobayashi also reported that addition of reagent **1** to the ylide derived from the bromide salt of α-thiazolium methyl acetate led to imidazo[2,-b]thiazoles (eq 24).[24] This constitutes a formal [4 + 1] cycloaddition. The loss of the methoxycarbonyl group occurred presumably through a decarboxylative pathway when using NaOMe. When NaH was used, formally 2 equiv of reagent **1** were incorporated.

Finally, triphenylphosphonium methylide could be added to reagent **1** to give a thioimidate substituted triphenylphosphonium methylide (eq 25).[25]

Addition of Other Activated Methylenes. Tominaga also embarked on a series of studies involving addition of activated



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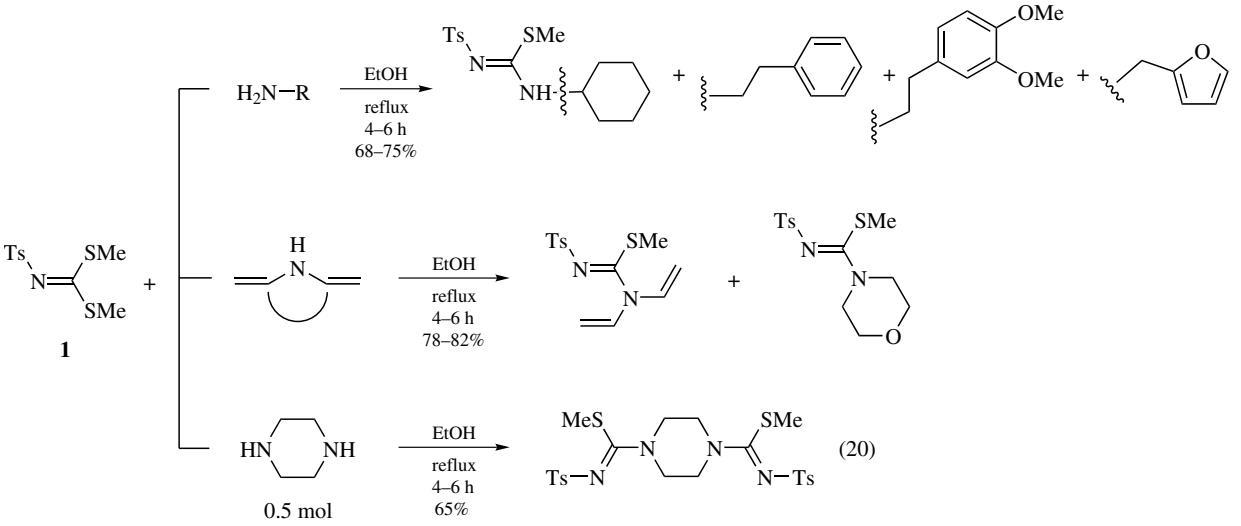
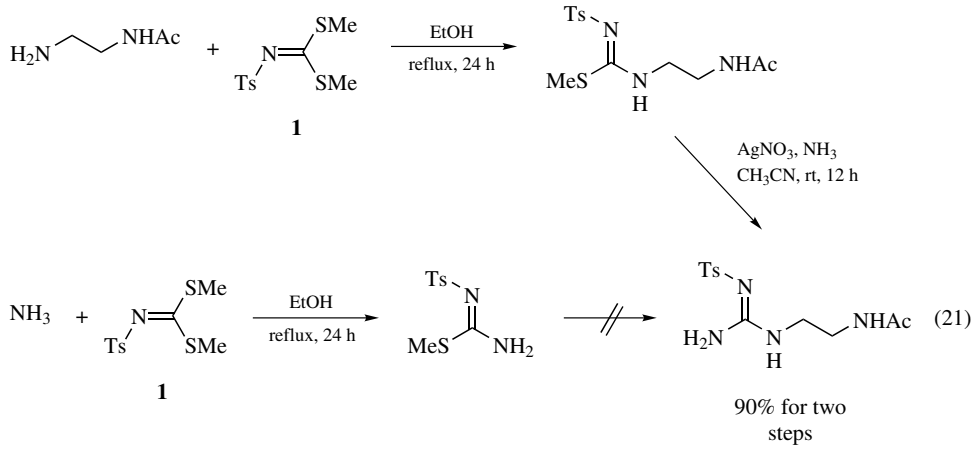
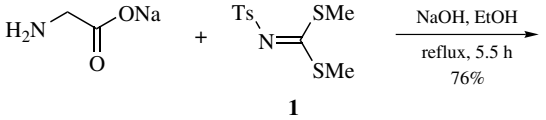


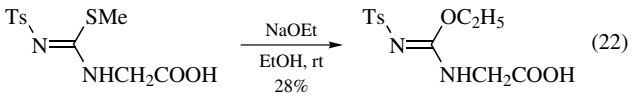


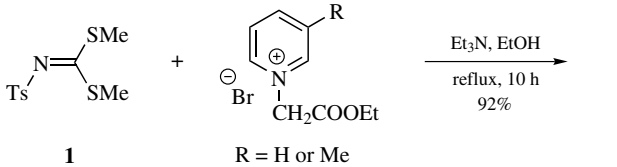
methylenes to **1**. These activated methylenes are substituted mostly α to the nitriles (eqs 26 and 27),[26,27] esters (eq 28),[28] or ketones (eqs 29 and 30).[29,30] Almost all of these reactions involved mono-addition of the carbanion intermediate to reagent **1** followed by elimination of one of the two SMe groups, leading to highly substituted push-pull types of enamides (substituted with electron donating and withdrawing groups at the two terminal olefinic carbons) which could be further transformed to various heterocycles such as pyrazoles (eq 26)[26] and isoquinolones and quinolones (eqs 27 and 28, respectively).[27,28]

Other examples are summarized in eqs 31–33. In particular, addition of the α-anion of *N*-nitrile imines to reagent **1** led to 2-amino pyrimidines (eq 31). The α-anion of α-phenyl nitromethane could also be added to reagent **1**, and subsequent hydrolysis of thioimidate intermediate gave amide-substituted nitro alkanes (eq 32).[31–33]

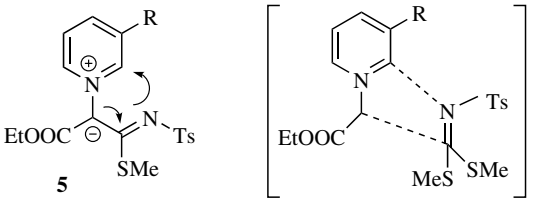
[3 + 2] Cycloadditions. Perhaps the most innovative use of **1** is the application in [3 + 2] cycloadditions that also was developed by Tominaga and Hosomi (eq 34).[34] Condensing reagent **1** with trimethylsilylmethyl amine or trimethylsilylmethanethiol in refluxing MeOH led to mono-addition products **6**. Treatment of **6a** (or **6b**) with CsF in MeCN at rt in the presence of ketones or aldehydes led to either 2-imino-oxazolidines or thiiranes.

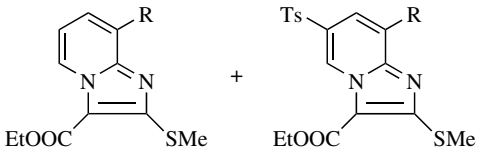




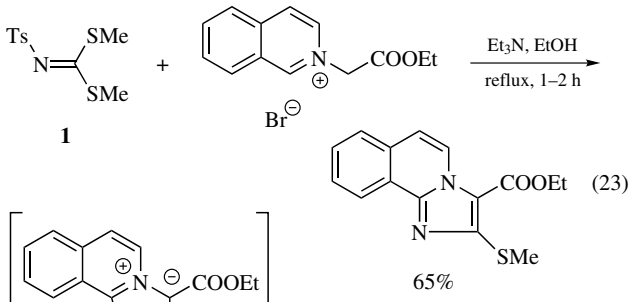


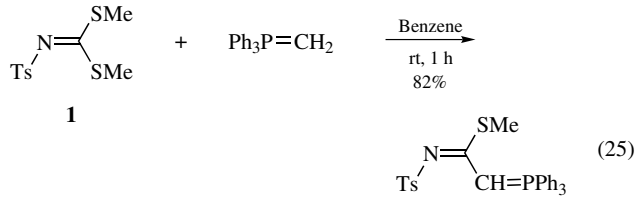
1 R = H or Me

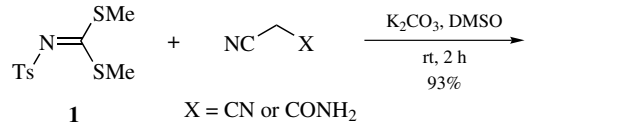


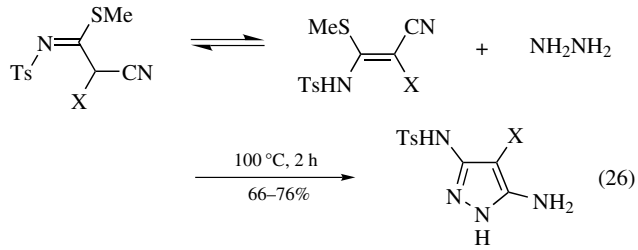


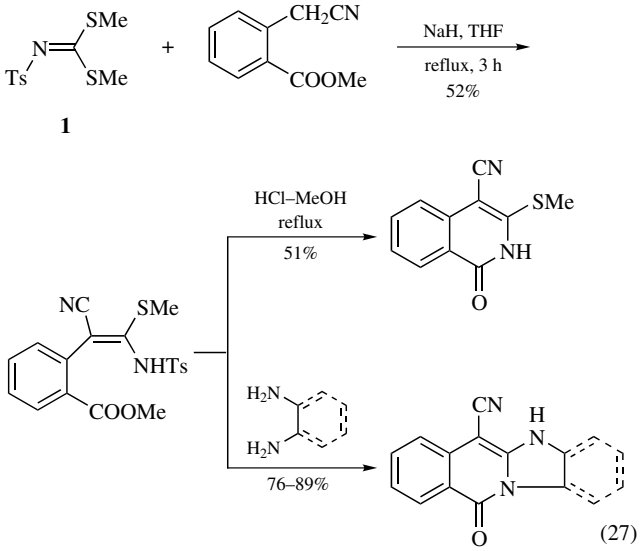
Conditions		Yield (%)
(a) xylene reflux, 30 h	7	38
(b) DMSO reflux, 20 h	35	0

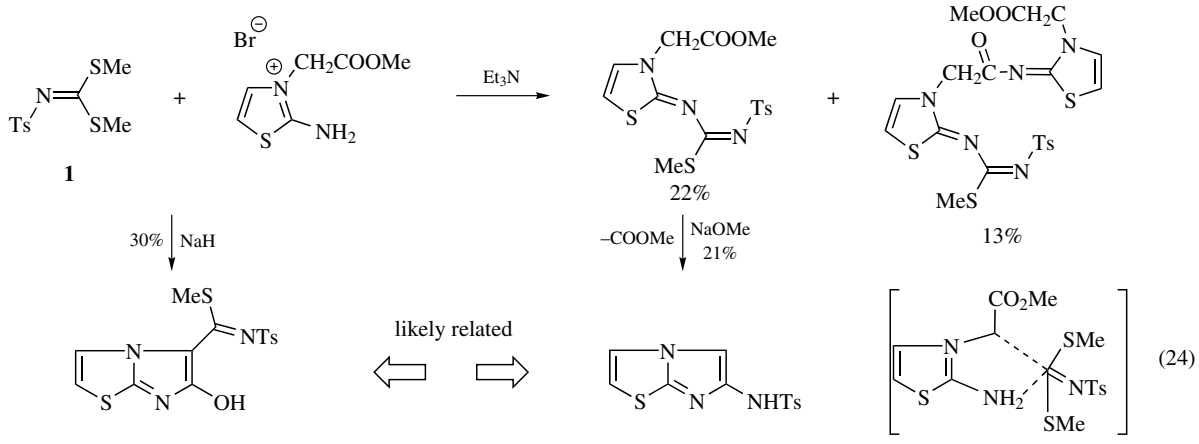


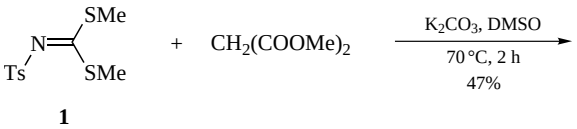












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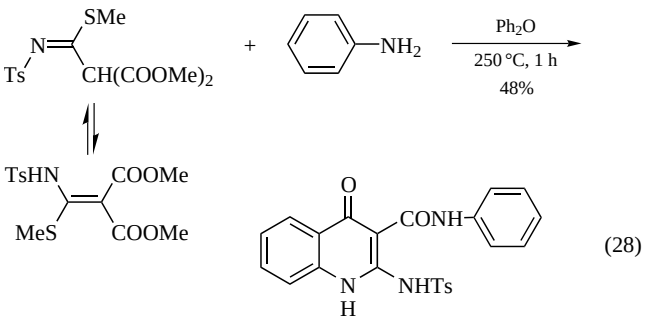

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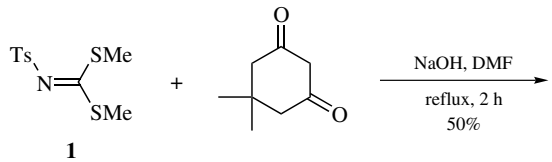

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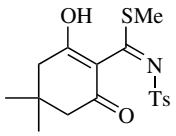

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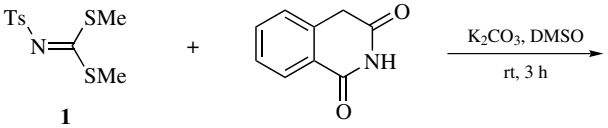

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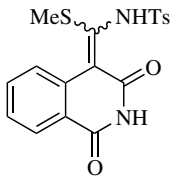

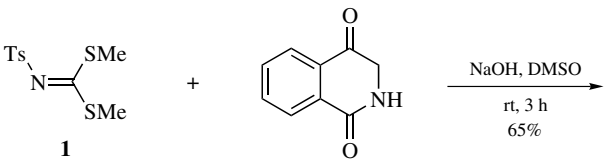

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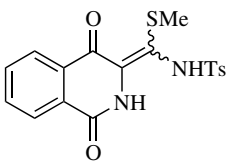

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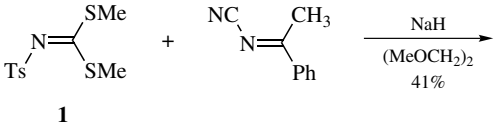

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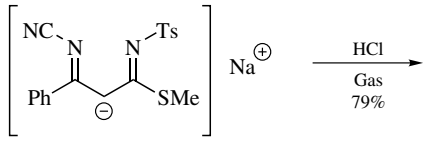

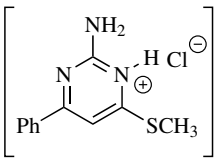

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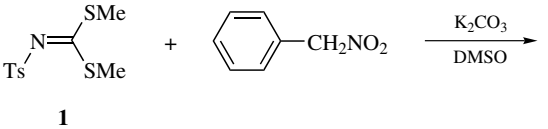

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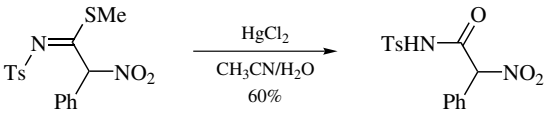

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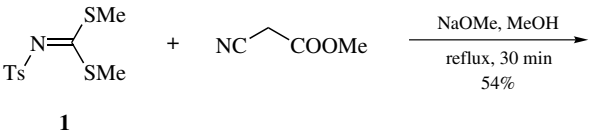

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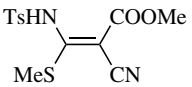
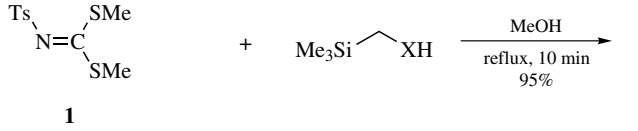


(33)

Mechanistically, desilylation of **6a** using CsF clearly led to anion **6c**. A loss of methylsulfide would lead to 1,3-dipolar intermediate **7a** that could be subsequently trapped with a ketone or an aldehyde in a [3+2] cycloaddition manner. This would then provide 2-imino-oxazolidines in a highly regioselective manner with a new stereocenter at the C5 position (eq 35).

On the other hand, CsF treatment of **6b** would lead to 1,3-dipolar intermediate **7b**. Subsequently, the initial [3+2] cycloadduct **8** undergoes fragmentation to give the observed thiiranes if pathway [a] occurs. When pathway [b] occurs with a simple loss of methylsulfide, 2-imino-thiazolidines can be isolated.



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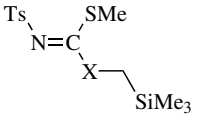
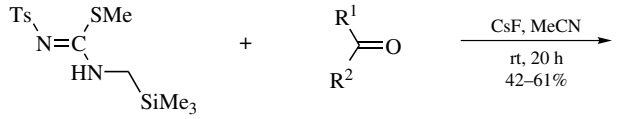
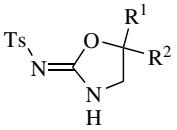


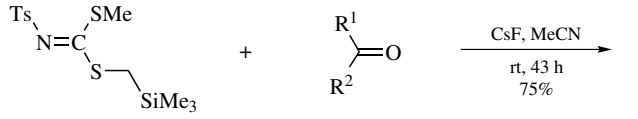
6

X = NH (**6a**) or S (**6b**)

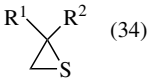


6a



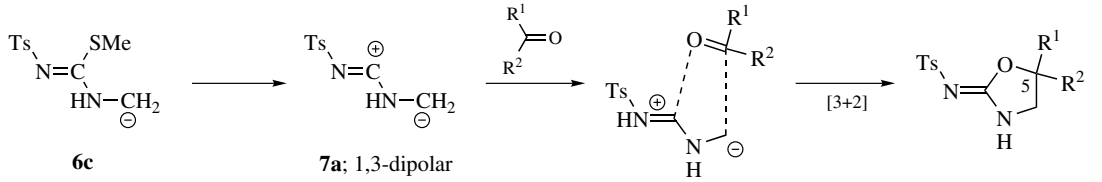


6b

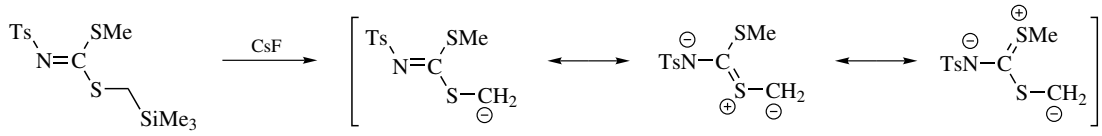


(34)

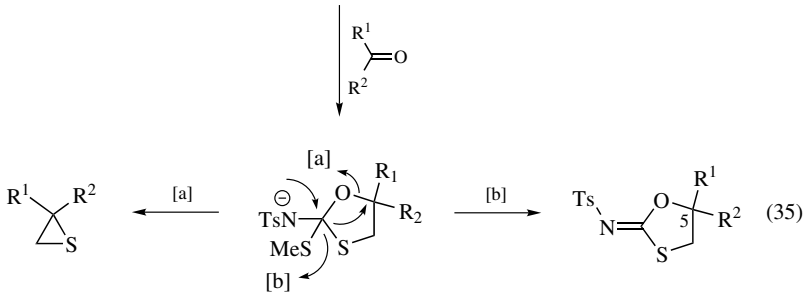
1. Kuwayama, Y.; Kataoka, S., *Yakugaku Zasshi* **1965**, *85*, 387.
2. (a) Gompper, R.; Hägele, W., *Chem. Ber.* **1966**, *99*, 2885. (b) Field, L.; Buckman, J. D., *J. Org. Chem.* **1968**, *33*, 3865.
3. Székely, Z.; Zakhariev, S.; Guarnaccia, C.; Antcheva, N.; Pongor, S., *Tetrahedron Lett.* **1999**, *40*, 4439.
4. Burgess, K.; Lim, D.; Ho, K. K.; Ke, C. Y., *J. Org. Chem.* **1994**, *59*, 2179.
5. Burgess, K.; Ho, K. K., *Tetrahedron Lett.* **1992**, *33*, 5677.
6. Vandendriessche, F.; Van Aerschot, A.; Voortmans, M.; Janssen, G.; Busson, R.; Van Overbeke, A.; Van den Bossche, W.; Hoogmartens, J.; Herdewijn, P., *J. Chem. Soc., Perkin Trans. 1* **1993**, *14*, 1567.
7. Vandendriessche, F.; Voortmans, M.; Hoogmartens, J.; Van Aerschot, A.; Herdewijn, P., *Bioorg. Med. Chem. Lett.* **1993**, *3*, 193.
8. Webb, T. R.; Eigenbrot, C., *J. Org. Chem.* **1991**, *56*, 3009.
9. (a) Bosin, T. R.; Hanson, R. N.; Rodricks, J. V.; Simpson, R. A.; Rapoport, H., *J. Org. Chem.* **1973**, *38*, 1591. (b) Neidlein, R.; Haussmann, W.; Heukelbach, E., *Chem. Ber.* **1966**, *99*, 1252. (c) Gompper, R.; Kunz, R., *Chem. Ber.* **1966**, *99*, 2900.
10. Fukada, N.; Takano, M.; Nakai, K.; Kuboike, S.; Takeda, Y., *Bull. Chem. Soc. Jpn.* **1993**, *66*, 148.
11. Wegner, M. M.; Rapoport, H., *J. Org. Chem.* **1977**, *42*, 3065.
12. Garín, J.; Meléndez, E.; Merchán, F. L.; Merino, P.; Orduna, J.; Tejero, T., *J. Heterocycl. Chem.* **1990**, *27*, 321.
13. Spindler, J., *Chem.-Zeitung* **1991**, *115*, 224.
14. Wakamiya, T.; Mizuno, K.; Ukita, T.; Teshima, T.; Shiba, T., *Bull. Chem. Soc. Jpn.* **1978**, *51*, 850.
15. Houghten, R. A.; Simpson, R. A.; Hanson, R. N.; Rapoport, H., *J. Org. Chem.* **1979**, *44*, 4536.
16. Ágai, B.; Doleschall, G.; Hornyák, G.; Lempert, K.; Simig, G., *Tetrahedron* **1976**, *32*, 839.
17. Modzelewska-Banachiewics, B.; Matosiuk, D., *Pharmazie* **1999**, *54*, 588.



6c **7a**; 1,3-dipolar



6b **7b**



8

(35)

Avoid Skin Contact with All Reagents

18. Ram, V. J.; Srivastava, P.; Singh, S. K.; Kandpal, M.; Tekwani, B. L., *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1087.
19. Maybhate, S. P.; Rajamohanan, P. P.; Rajappa, S., *Synthesis* **1991**, *3*, 220.
20. Seshadri, S.; Sanghavi, N. M.; Naik, R. V.; Tawate, S. R.; Trivedi, M. N.; Fruitwala, M. A., *India. J. Chem.* **1993**, *32B*, 688.
21. Barker, P. L.; Gendler, P. L.; Rapoport, H., *J. Org. Chem.* **1981**, *46*, 2455.
22. Gante, J., *Chem. Ber.* **1968**, *101*, 1195.
23. (a) Tominaga, Y.; Motokawa, S.; Shiroshita, Y.; Hosomi, A., *J. Heterocycl. Chem.* **1987**, *24*, 1365. (b) Fujito, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G., *Heterocycles* **1976**, *4*, 939.
24. Kurata, K.; Awaya, H.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G., *Yakugaku Zasshi* **1981**, *101*, 991.
25. Yoshida, H.; Ogata, T.; Inokawa, S., *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3315.
26. Tominaga, Y.; Hara, M.; Honkawa, H.; Hosomi, A., *J. Heterocycl. Chem.* **1990**, *27*, 1245.
27. Tominaga, Y.; Hidaki, S.; Matsuda, Y.; Kobayashi, G.; Sakemi, K., *Yakugaku Zasshi* **1980**, *100*, 456.
28. Tominaga, Y.; Michioka, T.; Moriyama, K.; Hosomi, A., *J. Heterocycl. Chem.* **1990**, *27*, 1217.
29. Hatada, T.; Sone, M.; Tominaga, Y.; Natsuki, R.; Matsuda, Y.; Kobayashi, G., *Yakugaku Zasshi* **1975**, *95*, 623.
30. Ueno, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G., *Chem. Pharm. Bull.* **1974**, *22*, 2624.
31. Hartke, K.; Sauerbier, M.; Richter, W. F., *Arch. Pharm.* **1992**, *325*, 279.
32. Maybhate, S. P.; Deshmukh A. R. A. S.; Rajappa, S., *Tetrahedron* **1991**, *47*, 3887.
33. Peseke, K., *Pharmazie* **1976**, *31*, 607.
34. (a) Tominaga, Y.; Ogata, K.; Ueda, H.; Kohra, S.; Hosomi, A., *Chem. Pharm. Bull.* **1995**, *43*, 1425. (b) Tominaga, Y.; Ueda, H.; Ogata, K.; Kohra, S.; Hojo, M.; Ohkuma, M.; Tomita, K.; Hosomi, A., *Tetrahedron Lett.* **1992**, *33*, 85. (c) Tominaga, Y.; Ogata, K.; Kohra, S.; Hojo, M.; Hosomi, A., *Tetrahedron Lett.* **1991**, *32*, 5987.

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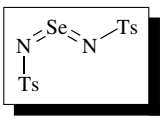
Bis[*N*-(*p*-toluenesulfonyl)]selenodiimide



[60123-29-7] $C_{14}H_{14}N_2O_4S_2Se$ (MW 417.36)
InChI = 1/C14H14N2O4S2Se/c1-11-3-7-13(8-4-11)21(17,18)
15-23-16-22(19,20)14-9-5-12(2)6-10-14/h3-10H,1-2H3
InChIKey = LWTNHQISFWPVLN-UHFFFAOYAC

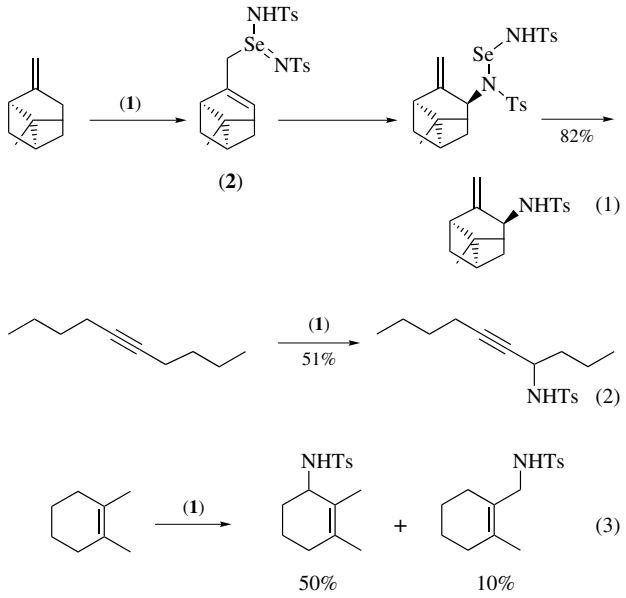
(allylic amination of alkenes and alkynes,[1] 1,2-diamination of 1,3-dienes[2])

Physical Data: mp 115–117 °C.

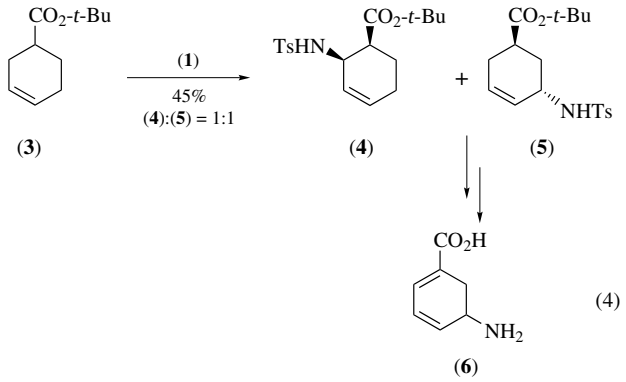
Preparative Methods: selenium metal is allowed to react with 2 equiv of anhydrous chloramine-*T* (TsNClNa) in $CHCl_2$ under N_2 for 24 h.[1] Also prepared by adding an ether solution of *N,N*-bis(trimethylsilyl)-*p*-toluenesulfonamide to an ether solution of selenyl chloride and stirring for 3 h.[3]

Handling, Storage, and Precautions: readily hydrolyzed by water; must be kept rigorously dry.

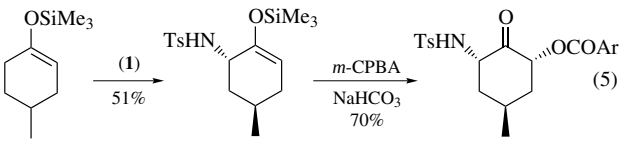
Allylic Amination and Diamination. The title compound (**1**) effects allylic amination of alkenes (eq 1)[1] and alkynes (eq 2).[1] The reaction occurs via an initial ene reaction to form (**2**) followed by a [2,3]-sigmatropic rearrangement. Nitrogen insertion takes place without net rearrangement of the double bond and generally occurs at the most substituted allylic position (eq 3).[1]

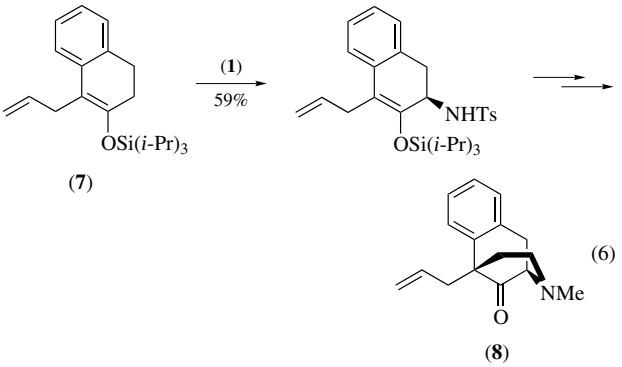


Compound (**1**) has been utilized in the total synthesis of gabaculine (**6**).[4] Upon treatment with (**1**), alkene (**3**) afforded a mixture of allylic amine derivatives (**4**) and (**5**) in 45% yield (eq 4). Compound (**1**) has also been used effectively in the syntheses of both β-apopicropodophyllin analogs[5] and daunosamine analogs.[6]



Trialkylsilyl enol ethers have also been aminated by (**1**), providing access to α-amino ketone derivatives (eq 5).[7] The products of the amination have the NHTs group in an axial orientation due to interactions between the π orbital and the σ^* orbital of the C–N bond.[8] Compound (**1**) was used to aminate silyl enol ether (**7**) in the synthesis of the benzomorphanone core structure (**8**) (eq 6).[9]



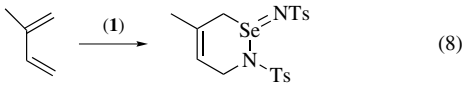


(7) (6) (8)

Compound (**1**), prepared from selenium oxychloride (**9**) and *N*,*N*-bis(trimethylsilyl)toluenesulfonamide (**10**) (eq 7), has been isolated and utilized in [4 + 2] cycloaddition reactions with dienes.[3] For example (**1**) reacts regioselectively with isoprene to yield 3,6-dihydro-1,2-selenazine (**11**) (eq 8).[3]

$$SeOCl_2 + p\text{-}MeC_6H_4SO_2N(TMS)_2 \longrightarrow (p\text{-}MeC_6H_4SO_2N)_2Se \quad (7)$$

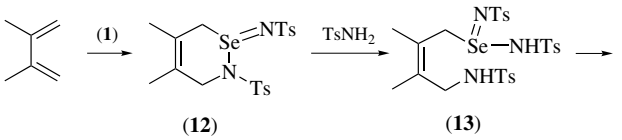
(**9**) (**10**) (**1**)



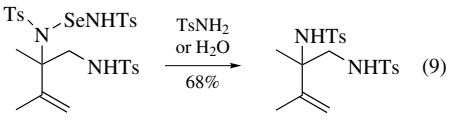
(8)

(**11**)

In cases where (**1**) is prepared from chloramine T, the reaction with 1,3-dienes directly produces 1,2-disulfonamides (eq 9).[2] rather than Diels–Alder adducts. Initially, the [4 + 2] adduct (**12**) is probably formed, which is then cleaved by traces of *p*-toluenesulfonamide to afford (**13**). This intermediate subsequently undergoes [2,3]-sigmatropic rearrangement to (**14**), which hydrolyzes in situ to yield disulfonamide (**15**). It has been suggested that the reagent prepared from selenium and chloramine T is actually $(TsNNa)_2SeCl_2$.[10] Cyclic dienes afford exclusively the *cis*-1,2-disulfonamides (eq 10).[2]

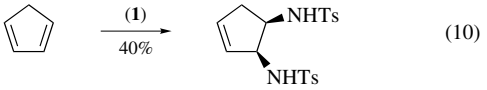


(**12**) (**13**)



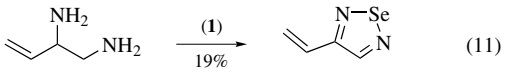
(9)

(**14**) (**15**)



(10)

Compound (**1**) has been used to prepare 3-vinyl-1,2,5-selenadiazole (**17**) from 1,2-diamine (**16**) via a cyclocondensation reaction (eq 11).[11]



(11)

(**16**) (**17**)

Related Reagents. Bis[*N*-(*p*-toluenesulfonyl)]sulfodiimide.

1. Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O., *J. Am. Chem. Soc.* **1976**, *98*, 269.
2. Sharpless, K. B.; Singer, S. P., *J. Org. Chem.* **1976**, *41*, 2504.
3. Barashenkov, G. G.; Derkach, N. Ya., *J. Org. Chem. USSR (Engl. Transl.)* **1986**, *22*, 1069.
4. Singer, S. P.; Sharpless, K. B., *J. Org. Chem.* **1978**, *43*, 1448.
5. Anjanamurthy, C.; Rai, K. M. L., *Indian J. Chem., Sect. B* **1985**, *24*, 505.
6. Dyong, I.; Wiemann, R., *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 682.
7. Magnus, P.; Mugrage, B., *J. Am. Chem. Soc.* **1990**, *112*, 462.
8. Magnus, P.; Lacour, J.; Bauta, W.; Mugrage, B.; Lynch, V., *J. Chem. Soc., Chem. Commun.* **1991**, 1362.
9. Magnus, P.; Coldham, I., *J. Am. Chem. Soc.* **1991**, *113*, 672.
10. Derkach, N. Ya.; Levchenko, E. S., *Russ. Chem. Rev. (Engl. Transl.)* **1989**, *58*, 507.
11. Bertini, V.; Lucchesini, F., *Synthesis* **1979**, 979.

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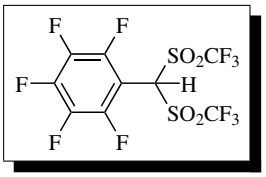
Pennsylvania State University, University Park, PA, USA

1-[Bis(trifluoromethanesulfonyl)methyl]-2,3,4,5,6-pentafluorobenzene[1]



[405074-81-9] $C_9HF_{11}O_4S_2$ (MW 446.21)

InChI = 1/C9HF11O4S2/c10-2-1(3(11)5(13)6(14)4(2)12)7(25(21,22)8(15,16)17)26(23,24)9(18,19)20/h7H

InChIKey = RLLDXJXYMKTGPV-UHFFFAOYAP

(an acid catalyst for organic transformations; an acid activator for chiral Lewis acid catalysts; a precursor for metal catalysts; a sterically bulky counter anion; a nucleophilically weak counter anion)

Physical Data: mp 86–87 °C; IR (KBr) 1522, 1501, 1347, 1321, 1198, 1127, 1024, 988, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21(br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.4, 98.0, 119.2 (q, 2C, J_{CF} = 330 Hz), 137.8 (d, 1C, J_{CF} = 258 Hz), 138.6 (d, 1C, J_{CF} = 257 Hz), 144.7 (d, 1C, J_{CF} = 264 Hz), 145.4 (d, 1C, J_{CF} = 262 Hz), 147.2 (d, 1C, J_{CF} = 262 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −157.9 (dt, 1F, J = 6.2, 21.5 Hz), −156.8 (dt, 1F, J = 6.2, 21.5 Hz), −142.6 (tt, 1F, J = 5.9, 21.5 Hz), −140.3 (br, 1F), −127.7 (ddd, 1F, J = 5.9, 15.2, 21.5 Hz), −75.2 (s, 6F).

Solubility: soluble in most organic solvents such as alcohols, acetonitrile, and dichloromethane.

Form Supplied in: white solid.

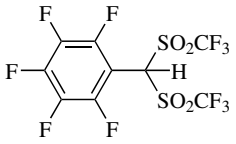
Preparative Method: To a solution of pentafluorobenzyl bromide (0.5 mmol) in dry Et_2O (3 mL) was added *t*-BuLi (0.34 mL, 0.55 mmol, 1.6 M solution in hexane) dropwise at −78 °C, and

the resulting mixture was stirred for 20 min. Triflic anhydride (92 μL, 0.55 mmol) was then added, and the resulting mixture was allowed to warm to room temperature over a period of 1 h. After the reaction mixture was cooled to −78 °C, *t*-BuLi (0.34 mL, 0.55 mmol, 1.6 M solution in hexane) was added dropwise, and the resulting mixture was stirred for 20 min. Triflic anhydride (0.55 mmol) was then added, and the resulting mixture was allowed to reach room temperature over a period of 1 h before the reaction was quenched with water. The resultant mixture was neutralized and washed with hexane. The aqueous phase was acidified with 4 M aqueous HCl and extracted with ether twice. The organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to bulb-to-bulb distillation.

Purification: recrystallization from hexane-AcOEt.

Handling, Storage, and Precautions: this compound is a stable solid in air, but is highly absorbent. Use of gloves and protective clothing is recommended.

Properties. 1-[Bis(trifluoromethanesulfonyl)methyl]-2,3,4,5,6-pentafluorobenzene (**1**) is one of the strongest Brønsted acids. Its pK_a value in CD_3CO_2D is 1.5 as measured by the ^{1}H NMR method.[1,2] It is stronger than sulfuric acid, which has a pK_a value of 7.0 as measured by the same method.

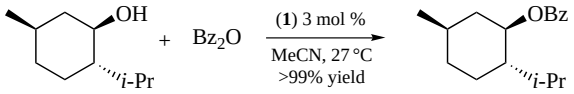


(**1**)

pK_a (CD_3CO_2D) 1.5

pK_a (CD_3CO_2D) 7.5

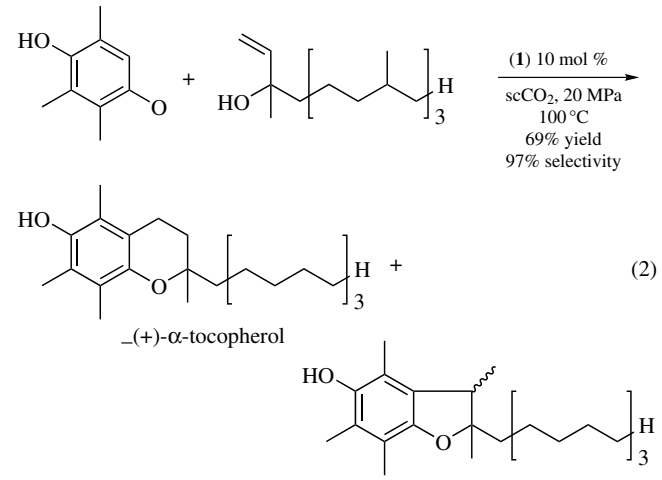
Benzoylation of (−)-Menthol. (−)-Menthol is benzoylated with benzoic anhydride using a catalytic quantity of (**1**) (eq 1).[3]



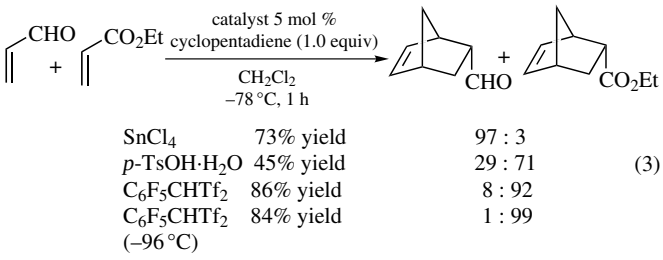
(1)

Synthesis of (±)-α-Tocopherol (Vitamin E) in $scCO_2$. (±)-α-Tocopherol (vitamin E) was synthesized by the condensation reaction of trimethylhydroquinone with isophytol in supercritical CO_2 ($scCO_2$) in the presence of (**1**) (eq 2).[4]

Chemoselective Diels–Alder Reaction with α,β-Unsaturated Aldehydes and Ketones. Brønsted acid (**1**) is an effective catalyst for the chemoselective Diels–Alder reaction of cyclopentadiene with acrolein and ethyl vinyl ketone (eq 3).[5] The reaction catalyzed by (**1**) proceeds smoothly and shows high chemoselectivity for ethyl vinyl ketone, although the catalytic activities of methanesulfonic acid and *p*-toluenesulfonic acid are poor. However, some Lewis acids such as $SnCl_4$ and $B(C_6F_5)_3$ show high chemoselectivity for acrolein.



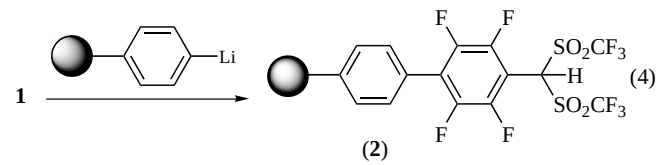
(2)



$SnCl_4$	73% yield	97 : 3
p-TsOH·H_2O	45% yield	29 : 71
$C_6F_5CHTf_2$	86% yield	8 : 92
$C_6F_5CHTf_2$ (–96 °C)	84% yield	1 : 99

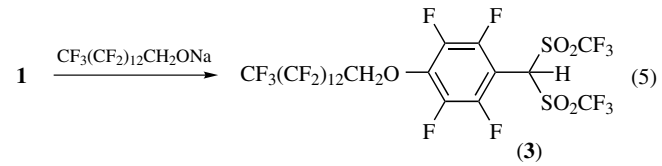
(3)

Design of Brønsted Acids. The nucleophilic *para*-substitution reaction occurs with some nucleophiles.[1] This makes it possible to design Brønsted acids such as polystyrene resin-bound Brønsted acid (**2**), fluorous Brønsted acid (**3**), and dibasic acid (**4**) (eqs 4–6).



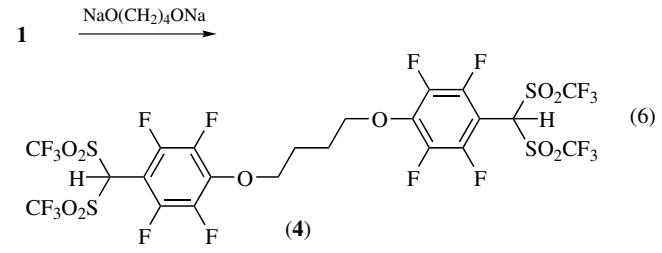
(4)

(**2**)



(5)

(**3**)

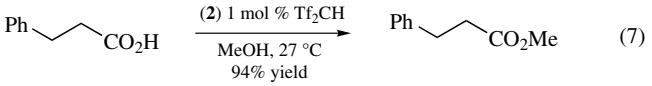


(6)

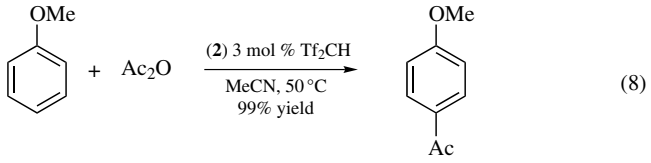
(**4**)

Highly Acidic Heterogeneous Catalyst. Both soluble Brønsted acid (**1**) and polystyrene resin-bound Brønsted acid (**2**) are widely used acid catalysts in many common acid-catalyzed

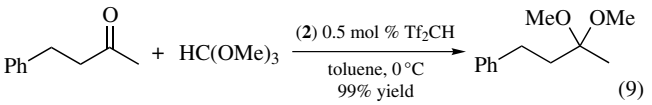
reactions, including esterification (eq 7), Friedel-Crafts acylation (eq 8), acetalization (eq 9), Mukaiyama aldol reaction (eq 10), and Sakurai–Hosomi allylation (eq 11).[3] The polymer catalyst (**2**) can be quantitatively recovered by filtration and reused.



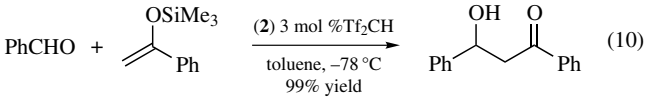
(7)



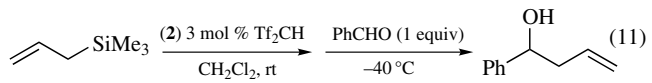
(8)



(9)

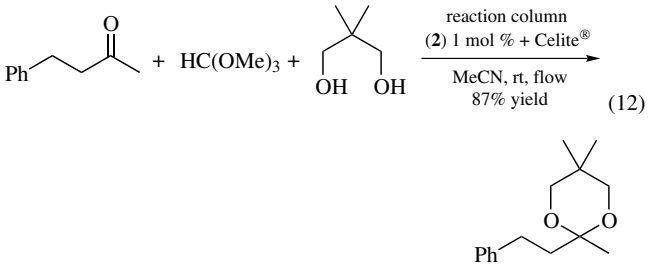


(10)

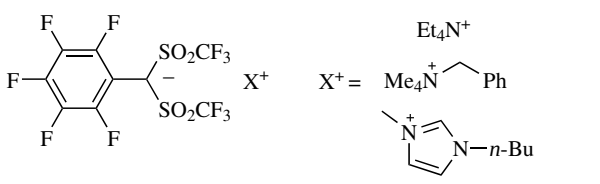


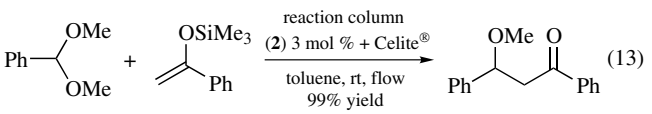
(11)

Furthermore, various acid-promoted reactions proceed to give the desired products in high yields by passing a solution of reactants through a reaction column packed with (**2**) and Celite® (eqs 12–14).[6] The polymer catalyst can be isolated from a mixture of (**2**) and Celite® based on the difference in their specific gravity: while (**2**) floats on water, Celite® sinks.

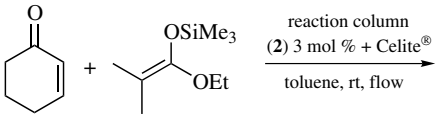


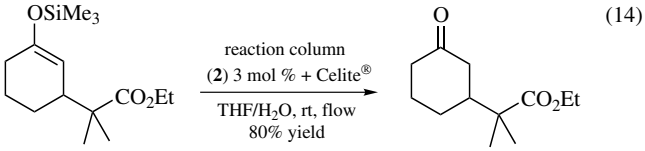
(12)





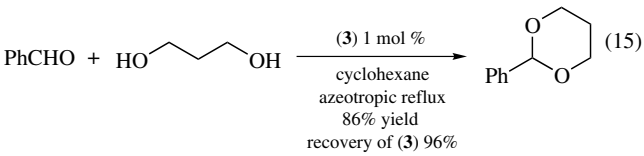
(13)



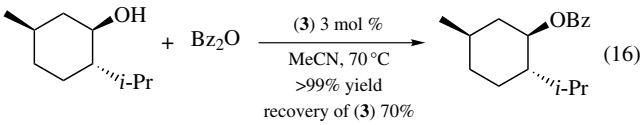


(14)

Fluorous Acid Catalyst. Fluorous catalysts are generally recycled by dissolving catalysts in a fluorous solvent that is not miscible with an organic solvent.[7] Recently, however, it has been shown that some fluorous catalysts do not need a fluorous solvent and can be recovered based on the use of temperature-dependent solubility in an organic solvent.[8,9] While (**1**) is soluble in most organic and fluorous solvents at any temperature, (**3**) appended to (**1**) by $OCH_2(CF_2)_nCF_3$ shows temperature-dependent solubility in some organic solvents.[10,11] Fluorous Brønsted acid (**3**) catalyzes acetalization (eq 15) and benzoylation (eq 16), and is soluble in an organic solvent under reaction conditions and can be recovered by precipitation at room temperature.

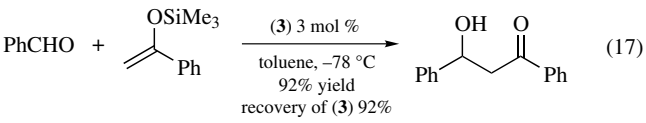


(15)



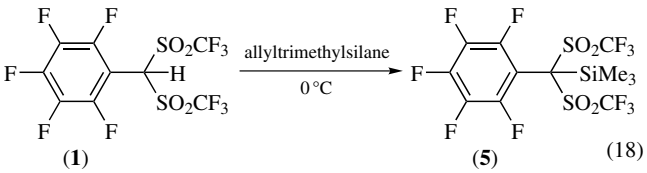
(16)

Moreover, (**3**) has high catalytic activity even under heterogeneous conditions (eq 17).



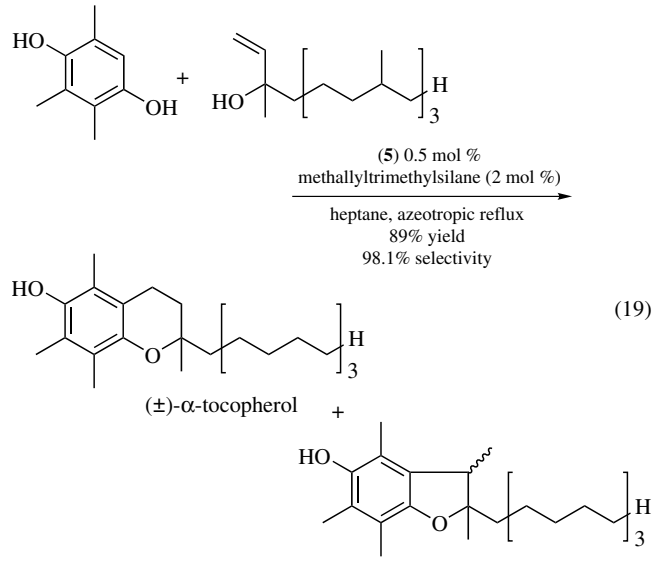
(17)

Application of Conjugate Base. Brønsted acid (**1**) is the starting material for the preparation of the super Lewis acid catalyst (**5**) (eq 18).[12]



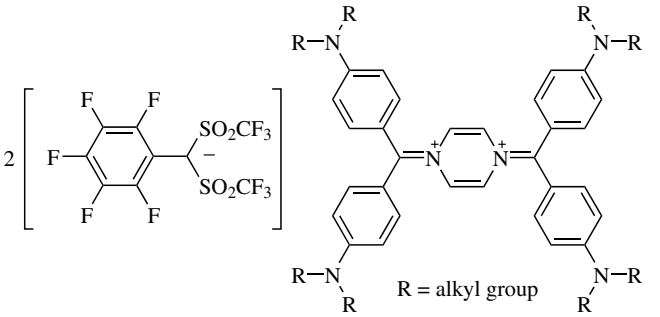
(18)

This catalyst is highly effective for the regioselective condensation of trimethylhydroquinone with isophytol to afford (±)-α-tocopherol (eq 19).[12]

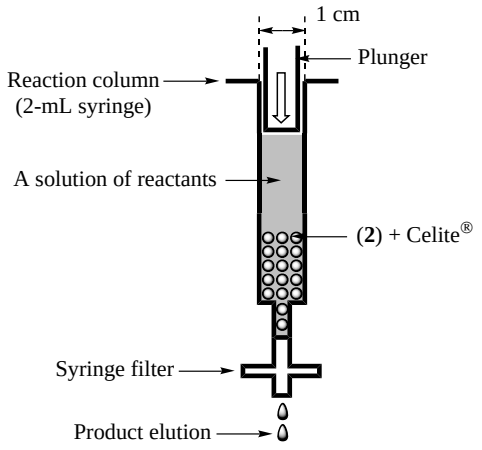


(19)

Brønsted acid (**1**) can be used for materials chemistry. The conjugate base of (**1**) is used as a counter anion of ionic liquids bearing quaternary ammonium, imidazolium, and pyridinium cations.[12] These ionic liquids are not only useful reaction solvents but also electrolytic solutions because of their low melting points, viscosity, and water solubility.

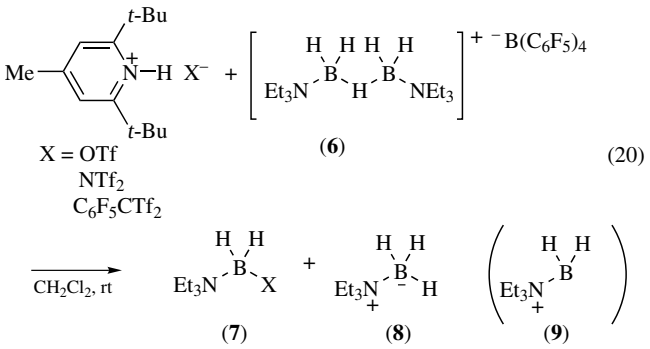


Diiminium compounds can be synthesized from the corresponding amine, silver nitrate, and (**1**). These are near-infrared ray-absorbing compounds, which are free from antimony and arsenic, and show excellent stability, particularly with regard to heat resistance, light stability, and moist heat resistance.[13]



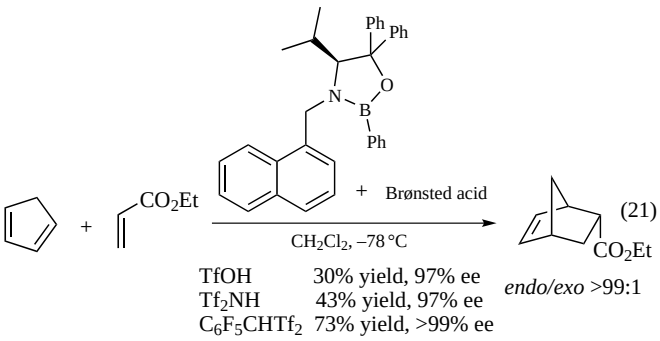
A polymer electrolyte is made from (**1**) supported on a polymer such as polystyrene. The film shows high proton condensation in the absence of water, thereby eliminating the need for a humidifier for a fuel cell gas.[14]

The conjugate base of (**1**) is also used as a weak nucleophile. The reactivity of hydride-bridged borane complex (**6**) with weak nucleophiles is attributed to the presence of a small amount of borenium ion (**9**). Some weak nucleophiles, $^{-}$OTf and $^{-}$NTf$_2$, which are conjugate bases of strong acids, can be used to demonstrate the presence of borenium ion. These two nucleophiles cleave the B–H–B bond. However, hydride-bridged borane complex is only partly converted to the corresponding tetravalent adduct (**7**) when conjugate base (**1**) is used (eq 20). In this case, unreacted borane complex (**8**) competes with weakly nucleophilic anion $^{-}$C(C$_6$F$_5$)Tf$_2$ for coordination into the unoccupied orbital of borenium ion (**9**).[15]



(20)

Brønsted Acid-activated Chiral Oxazaborolidine. The regio- and enantioselective Diels–Alder reaction of 1- and 2-substituted cyclopentadienes catalyzed by chiral oxazaborolidine is activated by (**1**).[16] Brønsted acid (**1**) is the most effective among various Brønsted acid activators (C$_6$F$_5$CHTf$_2$ > Tf$_2$NH > TfOH). This trend indicates that the larger steric dimensions of the counter anion confer reactivity, presumably due to its lower capacity to coordinate to boron, rather than pK_a of the Brønsted acid (eq 21).[3,17]



(21)

Related Reagents. Trifluoromethanesulfonic Acid; Trifluoromethanesulfonimide; Bis(trifluoromethanesulfonyl)methane; Tris(trifluoromethanesulfonyl)methane; [Bis(trifluoromethanesulfonyl)methyl]benzene.

1. Hasegawa, A.; Ishikawa, T.; Ishihara, K.; Yamamoto, H., *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1401.

2. Rode, B. M.; Engelbrecht, A.; Schantl, J., *Z. Phys. Chem.* **1973**, *253*, 17.
3. Ishihara, K.; Hasegawa, A.; Yamamoto, H., *Angew. Chem., Int. Ed.* **2001**, *40*, 4077.
4. Kokubo, Y.; Hasegawa, A.; Kuwata, S.; Ishihara, K.; Yamamoto, H.; Ikariya, T., *Adv. Synth. Catal.* **2005**, *347*, 220.
5. Nakashima, D.; Yamamoto, H., *Org. Lett.* **2005**, *7*, 1251.
6. Ishihara, K.; Hasegawa, A.; Yamamoto, H., *Synlett* **2002**, 1296.
7. (a) Horváth, I. T., *Acc. Chem. Res.* **1998**, *31*, 641. (b) Cavazzini, M.; Montanari, F.; Pozzi, G.; Quici, S., *J. Fluorine Chem.* **1999**, *94*, 183. (c) Bhattacharyya, P.; Croxtall, B.; Fawcett, J.; Gudmunsen, D.; Hope, E. G.; Kemmitt, R. D. W.; Paige, D. R.; Srauart, A. M.; Wood, D. R. W., *J. Fluorine Chem.* **2000**, *101*, 247.
8. Ishihara, K.; Kondo, S.; Yamamoto, H., *Synlett* **2001**, 1371.
9. Wende, M.; Meier, R.; Gladysz, J. A., *J. Am. Chem. Soc.* **2001**, *123*, 11490.
10. Ishihara, K.; Hasegawa, A.; Yamamoto, H., *Synlett* **2002**, 1299.
11. (a) Ishihara, K.; Yamamoto, H. In *Handbook of Fluorous Chemistry*; Gladysz, J. A.; Curran., D. P., Horváth, I. T., Eds.; Wiley: Weinheim, 2004; p 386. (b) Ishihara, K.; Hasegawa, A.; Yamamoto, H., *Angew. Chem., Int. Ed.* **2003**, *42*, 5731.
12. Suzuki, N.; Toda, N.; Kato, K.; Onosawa, T.; Tahara, K., *Jpn. Pat.* 2004307446 (2004).
13. Kurata, T., WO 2006120888 (2006).
14. Tsuzuki, T.; Nakajima, K.; Yamamoto, T.; Ishihara, K., *Jpn. Pat.* 2003272665 (2003).
15. Vreis, T. S. D.; Vedejs, E., *Organometallics* **2007**, *26*, 3079.
16. (a) Li, P.; Payette, J. N.; Yamamoto, H., *J. Am. Chem. Soc.* **2007**, *129*, 9534. (b) Payette, J. N.; Yamamoto, H., *J. Am. Chem. Soc.* **2007**, *129*, 9536.
17. Mathieu, B.; Ghosez, L., *Tetrahedron* **2002**, *58*, 8219.

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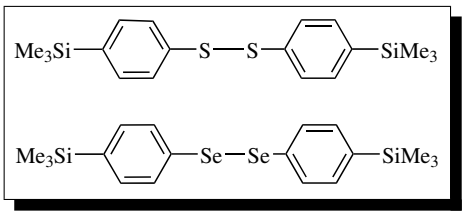
Bis(4-trimethylsilylphenyl) Disulfide and Bis(4-trimethylsilylphenyl) Diselenide



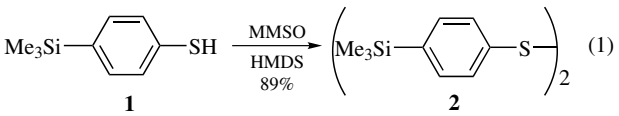
X = S
[18546-89-9] $C_{18}H_{26}S_2Si_2$ (MW 362.70)
InChI = 1/C18H26S2Si2/c1-21(2,3)17-11-7-15(8-12-17)19-20-16-9-13-18(14-10-16)22(4,5)6/h7-14H,1-6H3
InChIKey = RNHDNEGPJOGBBX-UHFFFAOYAF

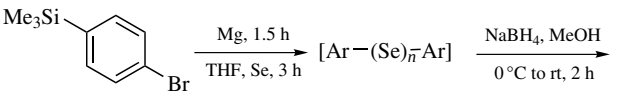
X = Se
[850185-96-5] $C_{18}H_{26}Se_2Si_2$ (MW 456.49)
InChI = 1/C18H26Se2Si2/c1-21(2,3)17-11-7-15(8-12-17)19-20-16-9-13-18(14-10-16)22(4,5)6/h7-14H,1-6H3
InChIKey = RLKJBTXPGJACLK-UHFFFAOYAM

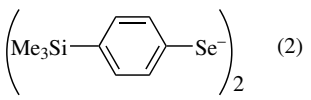
(reagents used as odorless replacements for diphenyl disulfide and diphenyl diselenide)

Physical Data: bis(4-trimethylsilylphenyl) disulfide is a colorless solid, mp 47–48 °C (hexane), and bis(4-trimethylsilylphenyl) diselenide is a yellow solid, mp 45 °C.

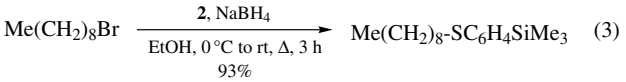
Preparative Methods: [1] the synthesis of bis(4-trimethylsilylphenyl) disulfide (**2**) involves oxidation of odorless 4-trimethylsilylthiophenol (**1**)[2a] with odorless methyl 6-morpholinohexyl sulfoxide (MMSO)[2b] in the presence of hexamethyldisilazane (HMDS) (eq 1). For the diselenide, 4-trimethylsilylphenylmagnesium bromide was reacted with selenium powder to provide the organoselenium intermediate **3**, which was then reduced with $NaBH_4$ in MeOH to afford the desired diselenide **4** in 65% overall yield (eq 2).

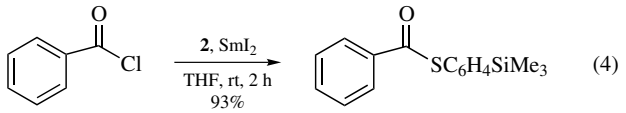


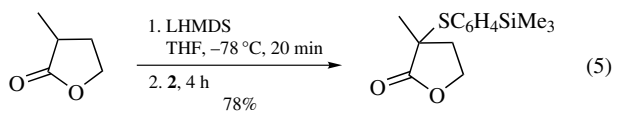


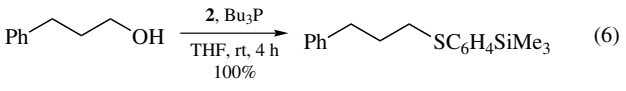


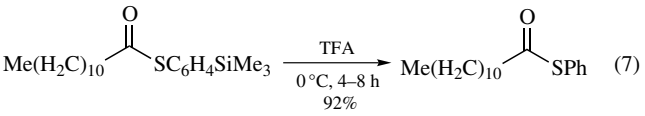
Selected Reactions of Bis(4-trimethylsilylphenyl) Disulfide (2).[1] Due to its odorless nature, the disulfide **2** is used as a replacement for diphenyl disulfide in various reactions. For example, nonyl bromide reacts with **2** in the presence of $NaBH_4$ to afford the expected sulfide (eq 3), and benzoyl chloride in the presence of samarium iodide gives the corresponding thioester (eq 4). The lithium enolate of 2-methyl-γ-lactone reacts with **2** to yield the corresponding α-sulfanylated lactone (eq 5), and the Hata reaction[3] of 3-phenylpropanol with **2** affords the corresponding sulfide (eq 6). In all of these cases, the product yields are comparable to those obtained using diphenyl disulfide. Finally, protodesilylation to generate the phenylthio derivatives can be conveniently carried out using TFA (eq 7).[2a]







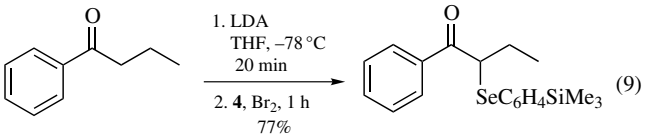




(7)

Selected Reactions of Bis(4-trimethylsilylphenyl) Diselenide (4).[1] The diselenide **4** is odorless in nature and finds use as a replacement for the odoriferous parent diphenyl diselenide in various reactions. For example, 1-bromodecane reacts with **4** in the presence of $NaBH_4$ to give the expected sulfide (eq 8), and the lithium enolate of 2-methyl-γ-lactone reacts with **4** to yield the corresponding α-selenylated lactone. However, the lithium enolate of butyrophenone reacts with the less electrophilic diselenide **4**, only after conversion to the selenyl bromide with bromine (eq 9). Following the procedure developed by Tiecco and coworkers,[4] the reaction of 4-pentenoic acid with diselenide **4** in the presence of DDQ yielded the corresponding lactone (eq 10). In all the cases, the product yields are comparable to those obtained using diphenyl diselenide. Finally, the oxidative elimination[5] of the selenium species can be carried out to generate the corresponding α,β-unsaturated compounds.

(8)



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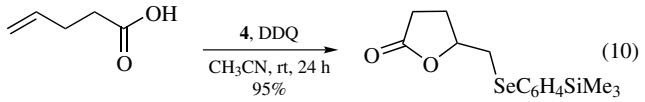
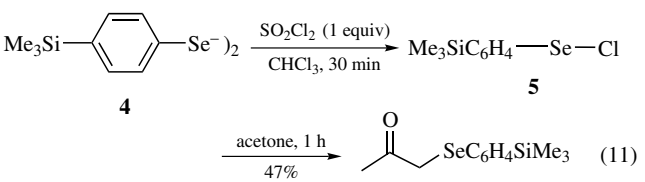
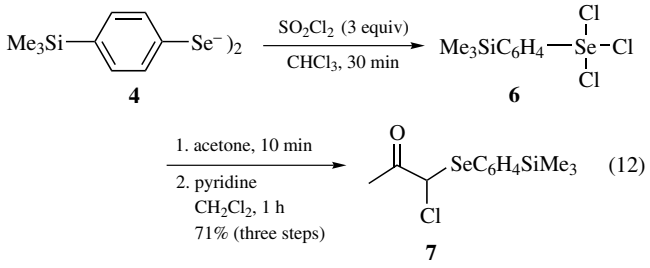


(10)

4-Trimethylsilylphenylselenium Chloride and Trichloride.[1] As phenylselenium chloride and the corresponding trichloride are well-known and useful reagents to introduce electrophilic selenium into organic molecules,[6,7] their odorless variants selenium chloride **5** and trichloride **6** have been investigated. Following a reported procedure,[7] compounds **5** and **6** were synthesized from diselenide **4** (eqs 11 and 12, respectively) using SO_2Cl_2. Although the corresponding selenyl bromide had to be prepared fresh before each reaction (eq 8), the chloride **5** could be stored under anhydrous conditions in a freezer (−20 °C). The corresponding selenium trichloride **6** was similarly stable and could be stored for several months at −20 °C. The α-selenylation reaction of acetone was performed by stirring freshly prepared chloride **5** in acetone (eq 11). Following a report by Engman and coworkers,[7b] the seleno-Pummerer reaction of acetone starting from diselenide **4** via the corresponding trichloride **6** afforded **7** (eq 12).



(11)



(12)

Related Reagents. Bis[4-(tridecafluorohexyl)phenyl] Diselenide; 1-(Butylseleno)-3,5-bis(heptadecafluorooctyl)-benzene; 1-(Butylseleno)-2,4-bis(heptadecafluorooctyl)benzene.

1. Patra, P. K.; Shanmugasundaram, K.; Matoba, M.; Nishide, K.; Kajimoto, T.; Node, M., *Synthesis* **2005**, 447.
2. (a) Nishide, K.; Miyamoto, T.; Kumar, K.; Ohsugi, S.; Node, M., *Tetrahedron Lett.* **2002**, *43*, 8569. (b) Nishide, K.; Patra, P. K.; Matoba, M.; Shanmugasundaram, K.; Node, M., *Green Chem.* **2004**, *6*, 142.
3. Skarzewski, J.; Gupta, A.; Wojaczynska, E.; Siedlecka, R., *Synlett* **2003**, 1615.
4. Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C., *Synlett* **2001**, 1767.
5. Reich, H. J.; Wollowitz, S., *Org. React.* **1993**, *44*, 1.
6. (a) Nicolaou, K. C.; Vega, J. A.; Vassilikogiannakis, G., *Angew. Chem., Int. Ed.* **2001**, *40*, 4441. (b) Marcos, I. S.; Cubillo, M. A.; Moro, R. F.; Diez, D.; Basabe, P.; Sanz, F.; Urones, J. G., *Tetrahedron Lett.* **2003**, *44*, 8831.
7. (a) Houllemare, D.; Ponthieux, S.; Outurquin, F.; Paulmier, C., *Synthesis* **1997**, 101. (b) Engman, L.; Persson, J.; Tilstam, U., *Tetrahedron Lett.* **1989**, *30*, 2665. (c) Engman, L., *J. Org. Chem.* **1988**, *53*, 4031.

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Boron Trifluoride–Dimethyl Sulfide[1]

$BF_3 \cdot SME_2$

[353-43-5] $C_2H_6BF_3S$ (MW 129.93)
InChI = 1/C2H6S.BF3/c1-3-2;2-1(3)4/h1-2H3;
InChIKey = BRWZPVRDOUWXKE-UHFFFAOYAF

(reagent for the cleavage of benzyl ethers and carbamates)

Physical Data: solid at −78 °C, liquid at rt; P_{satn}(25 °C) 217 mmHg.[2a]

Solubility: sol most organic solvents such as pentane.

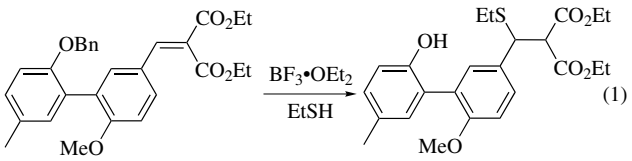
Form Supplied in: liquid complex sealed under nitrogen; commercially available.

Preparative Methods: made by the addition of equimolar amounts of the two components at −78 °C.[2a] Dissociation of the complex reported as 96.2% at 12 °C and 97.4% at 34 °C.[2a] Also formed when crystalline bromodimethylsulfonium tetrafluoroborate is aspirated at rt to give a colorless product without change in crystal form.[2b] The reagent system is normally assembled by adding a large excess of dimethyl sulfide to an excess of boron trifluoride etherate.[2c]

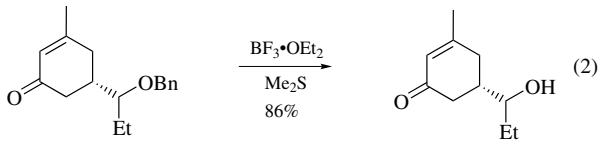
Handling, Storage, and Precautions: moisture-sensitive; use with carefully dried apparatus. All work must be carried out in an efficient fume hood.

Introduction. A number of boron trifluoride-type reagents have been used for the cleavage of ethers and related compounds, and a review of the earlier work on ether cleavage exists.[3] Carbon–oxygen bond cleavage using boron trifluoride combined with a sulfide or a thiol is based on the principle that a hard acid will interact with the oxygen and that the sulfur, being a soft nucleophile, will attack carbon. Small variations in the balance between the electrophilic and nucleophilic components can result in important changes in reactivity. Although the boron trifluoride–dimethyl sulfide complex is commercially available, the majority of the work reported has used boron trifluoride etherate in combination with dimethyl sulfide.[2c] A number of related reagent systems are compared in this entry. It will be seen that, although boron trifluoride together with a thiol can cause ether cleavage, there are certain functionalities, notably the carbonyl group in aldehydes and ketones and the alkene residue in α,β-unsaturated esters, that are themselves reactive to the system. The reagent system aluminum chloride ethanethiol (or dialkyl sulfide) is much more reactive than the boron-based systems and is thereby less selective.[4] For example, aluminum chloride in the presence of ethanethiol demethylates methyl ethers and cleaves methylenedioxy derivatives,[4b] but it also dehalogenates *o*- and *p*-bromoanisole in addition to cleaving the ether.[4e] Ethyl 4-bromobenzoate gives the acid in 92.5% yield using aluminum chloride–dimethyl sulfide.[4d] On the other hand, the system which uses aluminum chloride and sodium iodide in acetonitrile has been used to demethylate aliphatic methyl ethers selectively in the presence of phenolic methyl ethers.[5] The use of aluminum chloride in the presence of *N,N*-dimethylaniline has been recommended recently as a reagent for the cleavage of benzyl and allyl ethers.[6] The regioselective debenzylation of poly-*O*-benzylated monosaccharides has been achieved using tin(IV) chloride and titanium(IV) chloride. Three appropriately located metal chelating groups are necessary for selective debenzylation to proceed.[7] Recent general reviews on the cleavage of ethers[8] and on the chemical deprotection of esters[9] have been published.

Dealkylation of Ethers. The combination of an aliphatic thiol such as ethanethiol and boron trifluoride etherate has been used to remove benzyl groups. However, although that method works well it does suffer from an incompatibility with certain functional groups.[2c] The presence of an α,β-unsaturated ester in the same molecule can result in Michael addition as well as debenzylation (eq 1).[10] Boron trifluoride in the presence of dimethyl sulfide, being a milder reagent, does not cause this type of complication, as shown in eq 2.[11]

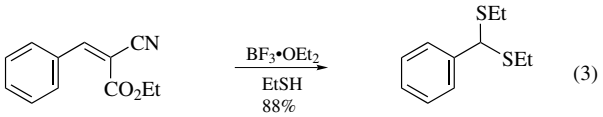


(1)

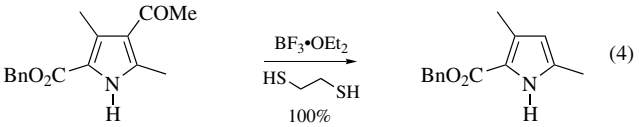


(2)

It is clear that boron trifluoride in the presence of a thiol will convert an aldehyde or ketone into the related thioacetal. For example, 4-benzyloxyacetophenone is converted into the ethyl thioacetal of 4-hydroxyacetophenone in 84% yield by $BF_3{\cdot}OEt_2$–EtSH, whereas using $BF_3{\cdot}OEt_2$–Me_2S gives 4-hydroxyacetophenone in 97% yield.[2c] The conversion of an acetal to a dithioacetal has also been reported using, for example 1,3-propanedithiol in the presence of BF_3; also known is the conversion of a dithiane into the related acyclic dithioacetal by using an excess of methanethiol and BF_3.[12] It has also been found that the double bond in substituted styrenes is cleaved by boron trifluoride etherate–ethanethiol when an electron-withdrawing group is present at the β-position (eq 3).[13] It is of interest to note that, although the system using a thiol does not result in benzyl ester cleavage, the removal of an acetyl group from a highly functionalized pyrrole has been reported (eq 4).[14]

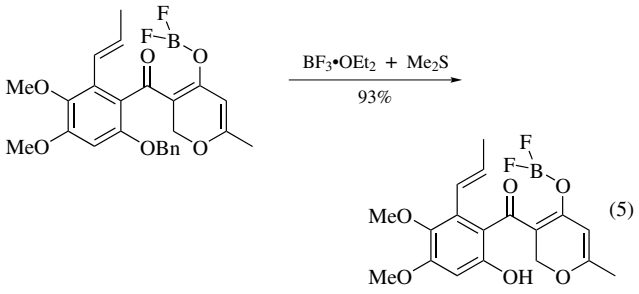


(3)



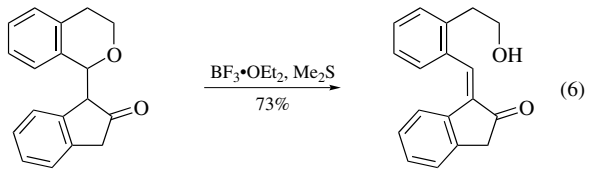
(4)

In a series of papers on the synthesis of benzopyrone derivatives, benzyl protection–deprotection of phenolic hydroxy groups has been a standard protocol.[15] It should be noted that in this series the yields of the debenzylated products are poor unless the boron difluoride complex is preformed. The example (eq 5) shown is part of a fulvic acid synthesis.[15c]

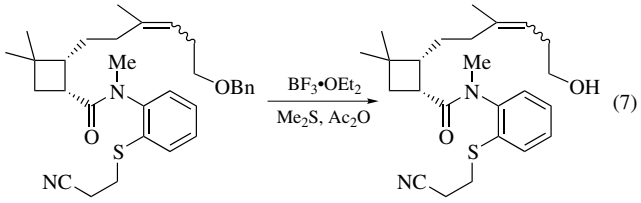


(5)

In the example shown in eq 6, the benzylic ether is part of a ring.[16] A number of other examples are recorded,[17] including cases where complex functionality and stereochemistry are unaffected by the procedure, as illustrated in eq 7[18]

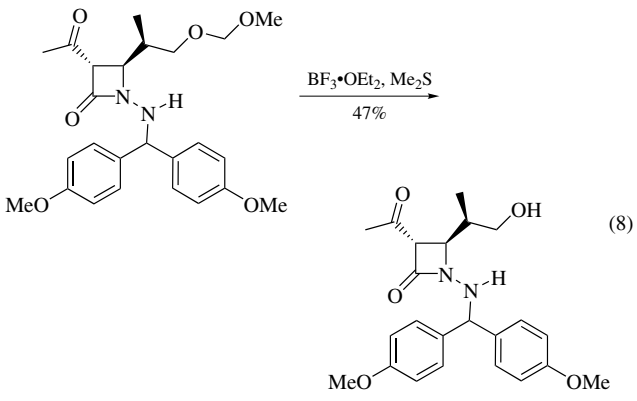


(6)

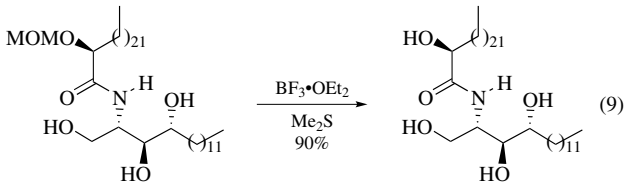


(7)

The method has also been used successfully to remove the methoxymethyl (MOM) group (eqs 8 and 9),[19,20] and should be compared once again with the use of boron trifluoride etherate–ethanedithiol (eq 10), which was used in a total synthesis of bruceantin.[21]



(8)



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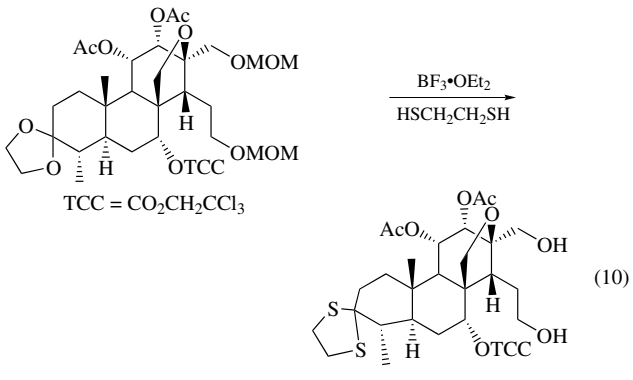
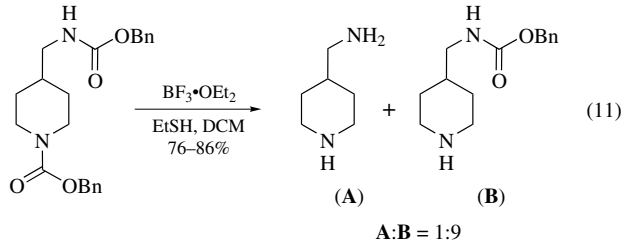


(10)

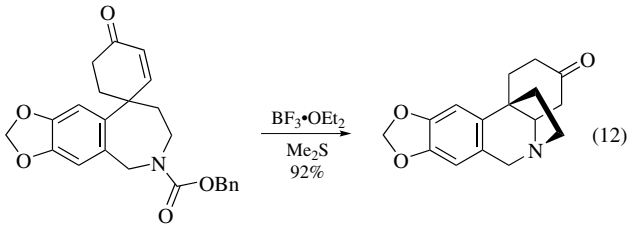
Cleavage of Benzyl Carbamates. The removal of the benzyloxycarbonyl (Cbz) group from nitrogen can be achieved successfully using boron trifluoride etherate in the presence of either a thiol or dimethyl sulfide. The carbamates derived from secondary amines are cleaved more rapidly than those from primary amines using the ethanethiol method, even when using $BF_3 \cdot OEt_2$ as the solvent. The procedure allows reasonable selectivity, as shown in eq 11.[10]

In another interesting example, the removal of the Cbz protecting group and concomitant intramolecular 1,4-addition of the resulting amine to the spiroenone gave racemic dihydrooxocrinine in a single operation (eq 12).[22]



(11)

A:**B** = 1:9



(12)

Related Reagents. Boron Trifluoride–Acetic Acid; Boron Trifluoride–Acetic Anhydride; Boron Trifluoride Etherate; Boron Trifluoride; Dimethyl Sulfide; Tetrafluoroboric Acid.

1. For a general review of the boron trihalides and their addition complexes, see: Greenwood, N. N., Thomas, B. S. In *Comprehensive Inorganic Chemistry*; Trotman-Dickenson, A. F., Ed.; Pergamon: New York, 1973; Vol. 1, p 956.
2. (a) Graham, W. A. G.; Stone, F. G. A., *J. Inorg. Nucl. Chem.* **1956**, *3*, 164; for a preliminary report, see: *Chem. Ind. (London)* **1956**, 319. (b) Böhme, H.; Boll, E., *Z. Anorg. Allg. Chem.* **1957**, *290*, 17. (c) Fuji, K.; Kawabata, T.; Fujita, E., *Chem. Pharm. Bull.* **1980**, *28*, 3662.
3. Meerwein, H., *Methoden Org. Chem. (Houben-Weyl)* **1965**, *6/3*, 143.
4. (a) Node, M.; Nishide, K.; Sai, M.; Fujita, E., *Tetrahedron Lett.* **1978**, 5211. (b) Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E., *Chem. Lett.* **1979**, 97. (c) Node, M.; Nishide, K.; Fuji, K.; Fujita, E., *J. Org. Chem.* **1980**, *45*, 4275. (d) Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E., *J. Org. Chem.* **1981**, *46*, 1991. (e) Node, M.; Kawabata, T.; Ohta, K.; Fujimoto, M.; Fujita, E.; Fuji, K., *J. Org. Chem.* **1984**, *49*, 3641.
5. Node, M.; Ohta, K.; Kajimoto, T.; Nishide, K.; Fujita, E.; Fuji, K., *Chem. Pharm. Bull.* **1983**, *31*, 4178.
6. Akiyama, T.; Hirofuji, H.; Ozaki, S., *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1932.
7. Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H., *J. Org. Chem.* **1989**, *54*, 1346.
8. Bhatt, M. V.; Kulkarni, S. U., *Synthesis* **1983**, 249.
9. Salomon, C. J.; Mata, E. G.; Mascaretti, O. A., *Tetrahedron* **1993**, *49*, 3691.
10. Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E., *J. Org. Chem.* **1979**, *44*, 1661.
11. Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F., *J. Am. Chem. Soc.* **1984**, *106*, 2455.
12. Sánchez, I. H.; Soria, J. J.; López, F. J.; Larraza, M. I.; Flores, H. J., *J. Org. Chem.* **1984**, *49*, 157.
13. (a) Fuji, K.; Kawabata, T.; Node, M.; Fujita, E., *Tetrahedron Lett.* **1981**, *22*, 875. (b) *J. Org. Chem.* **1984**, *49*, 3214.
14. Smith, K. M.; Langry, K. C., *J. Chem. Soc., Chem. Commun.* **1981**, 283.
15. (a) Yamauchi, M.; Katayama, S.; Nakashita, Y.; Watanabe, T., *J. Chem. Soc., Chem. Commun.* **1983**, 335. (b) Yamauchi, M.; Katayama, S.; Nakashita, Y.; Watanabe, T., *J. Chem. Soc., Perkin Trans. 1* **1985**, 183.

(c) Yamauchi, M.; Katayama, S.; Todoroki, T.; Watanabe, T., *J. Chem. Soc., Perkin Trans. 1* **1987**, 389. (d) Yamauchi, M.; Katayama, S.; Watanabe, T., *J. Chem. Soc., Perkin Trans. 1* **1987**, 395.

16. Hashigaki, K.; Yoshioka, S.; Yamoto, M., *Synthesis* **1986**, 1004.
17. (a) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodríguez, M.; Bosch, J., *J. Org. Chem.* **1987**, *52*, 267. (b) Engler, T. A.; Combrink, K. D.; Ray, J. E., *J. Am. Chem. Soc.* **1988**, *110*, 7931. (c) Yadav, J. S.; Sreenivasa Rao, E.; Sreenivasa Rao, V., *Synth. Commun.* **1989**, *19*, 705. (d) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander Velde, D., *J. Org. Chem.* **1990**, *55*, 1248. (e) Diez, A.; Vila, C.; Sinibaldi, M.-E.; Troin, Y.; Rubiralta, M., *Tetrahedron Lett.* **1993**, *34*, 733.
18. Ohtsuka, Y.; Niitsuma, S.; Tadokoro, H.; Hayashi, T.; Oishi, T., *J. Org. Chem.* **1984**, *49*, 2326.
19. Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M., *Tetrahedron* **1988**, *44*, 2149.
20. Sugiyama, S.; Honda, M.; Higuchi, R.; Komori, T., *Liebigs Ann. Chem.* **1991**, 349.
21. Sasaki, M.; Murae, T.; Takahashi, T., *J. Org. Chem.* **1990**, *55*, 528.
22. Sánchez, I. H.; López, F. J.; Soria, J. J.; Larraza, M. I.; Flores, H. J., *J. Am. Chem. Soc.* **1983**, *105*, 7640.

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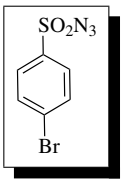
4-Bromobenzenesulfonyl Azide

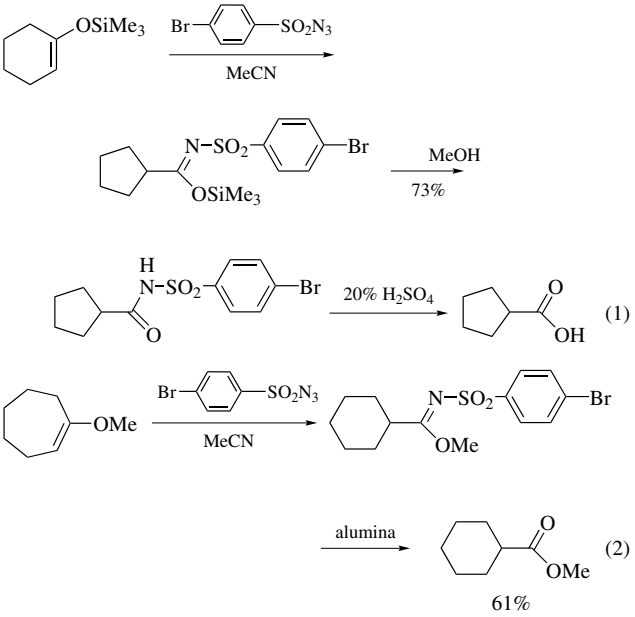


[6647-76-3] $C_6H_4BrN_3O_2S$ (MW 262.08)
InChI = 1/C6H4BrN3O2S/c7-5-1-3-6(4-2-5)13(11,12)10-9-8/h1-4H
InChIKey = GXMBSYQFGJYUBQ-UHFFFAOYAY

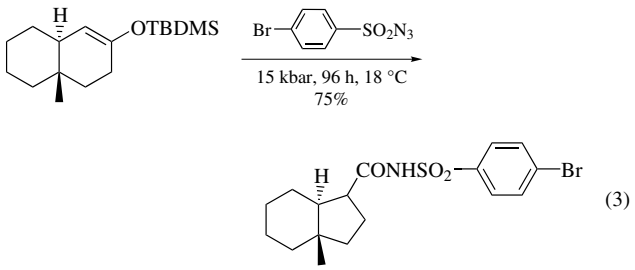
(1,3-dipolar reagent that undergoes cycloaddition to vinyl and alkynyl ethers[1])

Physical Data: mp 54.5–56 °C.
Solubility: sol most organic solvents.
Preparative Method: by the reaction of 4-bromobenzenesulfonyl chloride with excess sodium azide in a water–ethanol mixture.[23]
Purification: crystallization from ethanol.
Handling, Storage, and Precaution: should be used in solution. Azides are prone to violent detonation upon thermal, electrical, and mechanical shock.

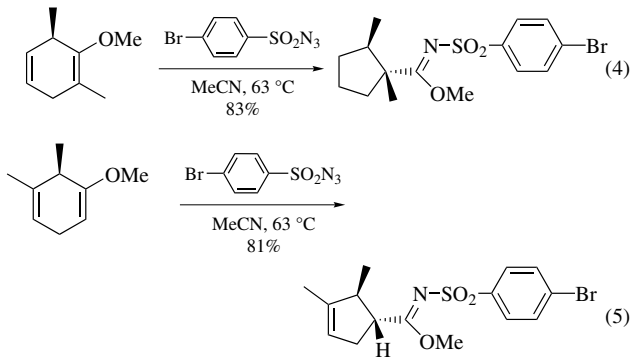
Dipolar Cycloaddition. The principal use of *p*-bromobenzenesulfonyl azide is in 1,3-dipolar cycloaddition reactions with functionally substituted alkenes. The reagent has been used at ambient temperature and pressure to convert simple trimethylsilyl[4] and methyl[5] enol ethers of cyclic ketones to ring-contracted *p*-bromobenzenesulfonimidates, and thence to the corresponding amides, esters, or acids (eqs 1 and 2).



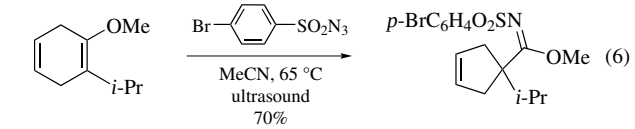
At high pressure (∼ kbar) the normally more sluggish *i*-butyldimethylsilyl enol ethers of cyclic ketones react in good yield to afford the ring contracted product (eq 3).[6,7]

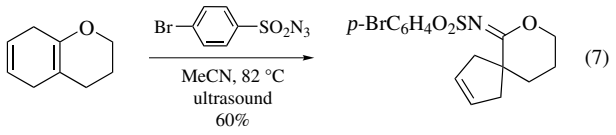


The chemo-, regio-, and stereoselectivity of the ring contraction process has been demonstrated with a variety of dienol ethers obtained by dissolving metal reduction of aromatic methyl ethers (eqs 4 and 5).[8]



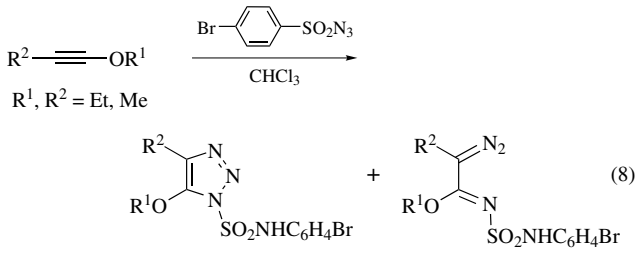
Methyl enol ethers which are unreactive under ambient conditions react in good yield to afford the corresponding *p*-bromobenzenesulfonimidates under the influence of low-wattage ultrasound (eqs 6 and 7).[9]





(7)

Cycloaddition of *p*-bromobenzenesulfonyl azide to alkynyl ethers affords equilibrium mixtures of triazole and diazocarboximidate. In the case of the ether in which both the carbon and the oxygen substituents of the alkynyl ether are methyl, only the triazole is found (eq 8).[10]



(8)

1. *1,3-Dipolar Cycloaddition Chemistry*; Lwowski, W., Ed.; Wiley: New York, 1984; Vol. 1, p 817.
2. Curtius, T., *J. Phys. Chem.* **1930**, *125*, 303.
3. Reagan, M. T.; Nickon, A., *J. Am. Chem. Soc.* **1968**, *90*, 4096.
4. Wohl, R. A., *Helv. Chim. Acta* **1973**, *56*, 1826.
5. Wohl, R. A., *Tetrahedron Lett.* **1973**, 3111.
6. Dauben, W. G.; Hart, D. J., *J. Org. Chem.* **1977**, *42*, 922.
7. Dauben, W. G.; Bunce, R. A., *J. Org. Chem.* **1982**, *47*, 5042.
8. Goldsmith, D. J.; Soria, J. J., *Tetrahedron Lett.* **1986**, *27*, 4701.
9. Goldsmith, D. J.; Soria, J. J., *Tetrahedron Lett.* **1991**, *32*, 2457.
10. Himbert, G.; Regitz, M., *Chem. Ber.* **1972**, *105*, 2963.

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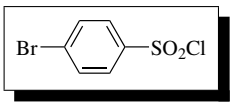
4-Bromobenzenesulfonyl Chloride

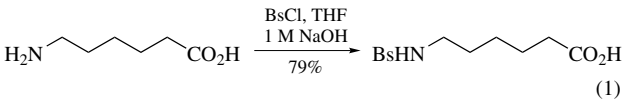


[98-58-8] $C_6H_4BrClO_2S$ (MW 225.52)
InChI = 1/C6H4BrClO2S/c7-5-1-3-6(4-2-5)11(8,9)10/h1-4H
InChIKey = KMMHZIBWCXYAAH-UHFFFAOYAQ

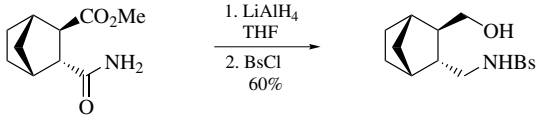
(N-protection of amines; formation of sulfonamides, sulfonate esters, and carbodiimides)

Alternate Name: BsCl.
Physical Data: mp 73–75 °C.
Solubility: sol Et_2O, THF, petroleum ether and 1,4-dioxane.
Preparative Method: reaction of sodium *p*-bromobenzenesulfonate with phosphorus(V) chloride gives a 90% yield.[1]
Handling, Storage, and Precautions: harmful by skin absorption and ingestion and causes burns. The reagent is moisture sensitive and will react with nucleophilic solvents, e.g. alcohols, liberating HCl and therefore should be stored under an inert atmosphere.

Protection of Nitrogen, Formation of Sulfonamides. *p*-Bromobenzenesulfonyl chloride (BsCl) has been widely used to N-protect amines (eqs 1 and 2).[2,3] Due to the relatively high molecular weight, *p*-bromobenzenesulfonyl derivatives have a higher melting point and may be more readily crystallizable than lower molecular weight derivatives.



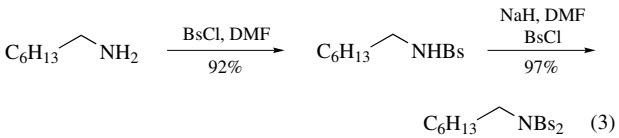
(1)



(2)

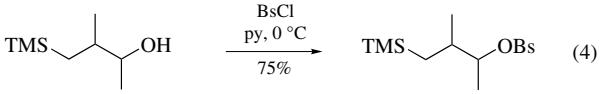
The electron-withdrawing nature of the *p*-bromobenzenesulfonyl group has been used, via the sulfonamide derivative of a pyridone, in inverse electron demand Diels–Alder reactions to great effect.[4]

Disulfonamides can be prepared from primary amines (eq 3), thereby converting the amine into a better leaving group.[5] The syntheses of sulfonamides derived from sulfamates have also been reported.[6]



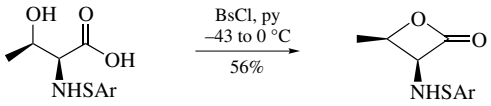
(3)

Formation of Sulfonate Esters. The reaction of hydroxy groups with *p*-bromobenzenesulfonyl chloride gives *p*-bromobenzenesulfonates (brosylates) (eq 4).[7] The brosylate ester transforms the hydroxy functional group into a good leaving group and this has been exploited in synthesis. Inositol derivatives[8] have been prepared using brosylates in preference to the corresponding 4-methylbenzenesulfonates, the latter being a less effective leaving group in this particular case.



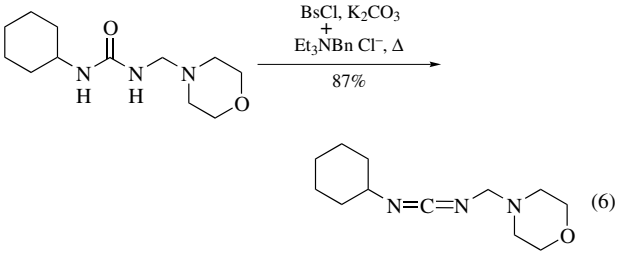
(4)

The reaction of β-hydroxy acids with *p*-bromobenzenesulfonyl chloride in the presence of a tertiary amine gives β-lactones (eq 5).[9,10] Brosylate esters of oximes have been manipulated in the Beckmann rearrangement of erythromycin derivatives[11] as an alternative to both 4-methylbenzenesulfonate esters and benzenesulfonate esters.



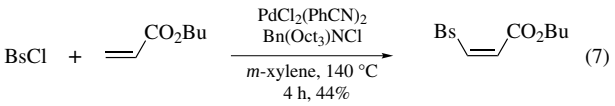
(5)

Formation of Carbodiimides. *p*-Bromobenzenesulfonyl chloride reacts with ureas to form carbodiimides in good yield (eq 6).[12]



(6)

Reaction with Alkenes and Arenes. *p*-Bromobenzenesulfonyl chloride will undergo desulfonylative coupling to alkenes and arenes using Pd^{II} catalysis (eq 7).[13]



(7)

1. Marvel, C. S.; Smith, F. E., *J. Am. Chem. Soc.* **1923**, *45*, 2696.
2. Pavlidis, V. H.; Chan, E. D.; Pennington, L.; McParland, M.; Whitehead, M.; Coutts, I. G. C., *Synth. Commun.* **1988**, *18*, 1615.
3. Hamanaka, N.; Seko, T.; Miyazuki, T.; Naka, M.; Furuta, K.; Yamamoto, H., *Tetrahedron Lett.* **1989**, *30*, 2399.
4. Posner, G. H.; Switzer, C., *J. Org. Chem.* **1987**, *52*, 1642.
5. (a) DeChristopher, P. J.; Adamek, J. P.; Lyon, G. D.; Klein, S. A.; Baumgarten, R. J., *J. Org. Chem.* **1974**, *39*, 3525. (b) DeChristopher, P. J.; Adamek, J. P.; Sanford, A. K.; Lyon, G. D.; Baumgarten, R. J., *J. Org. Chem.* **1975**, *40*, 3288.
6. Spillane, W. J.; Burke, P. O., *Synthesis* **1986**, 1021.
7. Shiner, V. J.; Ensinger, M. W.; Huffmann, J. C., *J. Am. Chem. Soc.* **1989**, *111*, 7199.
8. Espelie, K. E.; Anderson, L., *Carbohydr. Res.* **1976**, *46*, 53.
9. Pu, Y.; Martin, F. M.; Vederas, J. C., *J. Org. Chem.* **1991**, *56*, 1280.
10. Pansare, S. V.; Vederas, J. C., *J. Org. Chem.* **1989**, *54*, 2311.
11. Djokic, S.; Kobrehel, G.; Lazarevski, G.; Lopotar, N.; Tamburasev, Z.; Kamenar, B.; Nagl, A.; Vickovic, I., *J. Chem. Soc., Perkin Trans. 1* **1986**, 1881.
12. Jaszay, Z. M.; Petnehazy, I.; Toke, L.; Szajani, B., *Synthesis* **1987**, 520.
13. Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M., *J. Chem. Soc., Perkin Trans. 1* **1990**, 2207.

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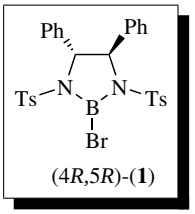
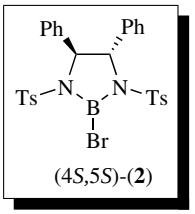
(4*R*,5*R*)-2-Bromo-1,3-bis-(4-methylphenyl sulfonyl)-4,5-diphenyl-1,3,2-diazaborolidine and (4*S*,5*S*)-2-Bromo-1,3-bis-(4-methylphenyl sulfonyl)-4,5-diphenyl-1,3,2-diazaborolidine



(4*R*,5*R*)-(**1**)

[121758-17-6] $C_{28}H_{26}BBrN_2O_4S_2$ (MW 609.36)
InChI = 1/C28H26BBrN2O4S2/c1-21-13-17-25(18-14-21)37(33,34)31-27(23-9-5-3-6-10-23)28(24-11-7-4-8-12-24)32(29(31)30)38(35,36)26-19-15-22(2)16-20-26/h3-20,27-28H,1-2H3/t27-,28-/m1/s1
InChIKey = PEEHKMHARMPWIU-VSGBNLITBC



(4*S*,5*S*)-(**2**)

[124600-99-3] $C_{28}H_{26}BBrN_2O_4S_2$ (MW 609.36)
InChI = 1/C28H26BBrN2O4S2/c1-21-13-17-25(18-14-21)37(33,34)31-27(23-9-5-3-6-10-23)28(24-11-7-4-8-12-24)32(29(31)30)38(35,36)26-19-15-22(2)16-20-26/h3-20,27-28H,1-2H3/t27-,28-/m0/s1
InChIKey = PEEHKMHARMPWIU-NSOVKSMOBN

(chiral bromoborane reagent used to control stereochemistry of enantioselective aromatic Claisen rearrangements, allylations of aldehydes, aldol reactions, and formation of chiral propa-1,2-dienyl and propargyl alcohols)

Alternate Names: 2-bromo-4,5-diphenyl-1,3-bis-(toluene-4-sulfonyl)-[1,3,2]diazaborolidine.

Physical Data: white solid.

Solubility: soluble in methylene chloride.

Preparative Methods: (1*R*,2*R*)−(+)-*N*,*N*′-bis-*p*-toluenesulfonyl-1,2-diphenylethylenediamine[1] was placed in a dry 25 mL round-bottom flask equipped with a magnetic stir bar and sealed with a septum. The flask was evacuated and flushed with argon three times. Freshly distilled dichloromethane (12 mL) was injected and the homogeneous solution was cooled to 0 °C for 10 min, warmed to 23 °C, kept at 23 °C for 40 min, and concentrated under vacuum (ca. 2 mm of Hg) using a metal tube inserted through the septum. Dryness of the vacuum line was maintained with a drying tube containing NaOH pellets and $CaSO_4$ to prevent possible hydrolysis of bromoborane **1**.[2]

Purification: solvent and HBr are removed under reduced pressure.

Handling, Storage, and Precautions: moisture sensitive.

Original Commentary

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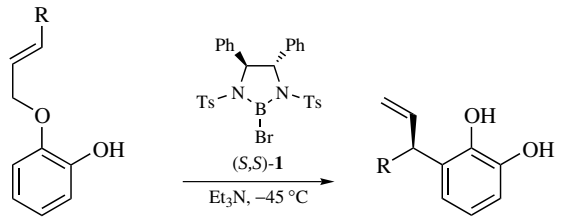
General. Chiral 2-bromo-1,3-bis(4-methylphenyl sulfonyl)-4,5-diphenyl-1,3,2-diazaborolidine (**1**) is used to control the stereochemistry of enantioselective aromatic Claisen rearrangements, allylations of aldehydes, aldol reactions, and formation of chiral propa-1,2-dienyl and propargyl alcohols. Included is the discussion of both the (*R,R*) and the (*S,S*) chiral controllers.

Enantioselective Aromatic Claisen Rearrangements. Chiral boron reagent (**1**) can facilitate Claisen rearrangement of catechol monoallylic ether derivatives (**2**), affording catechol adducts (**3**)[3] (eq 1). Products formed by rearrangement of the allylic moiety to the *para* position and by abnormal Claisen rearrangement are not detected.



(**2**) (**3**) (1)

89–97% yield
94–95% ee

Rearrangement of a (*Z*)-allylic moiety requires higher reaction temperatures than do the corresponding (*E*)-allylic ethers, but affords *ent*-**3** in comparable yields and percent ee's. Trisubstituted allylic ether derivatives also afford benzofuran derivatives.

Replacement of the aromatic substituent of ligand **1** with 3,5-bis(trifluoromethyl)phenyl group increases the rate of reaction, but slightly lowers the enantioselectivity.

These reactions do not proceed in the absence of a hydroxy group in the *ortho* position. Thus, it is suggested that a rigid five-membered cyclic intermediate is formed (Figure 1). Reaction of catechol monoallylic ethers with **1** does not significantly decrease the Lewis acidity of the boron atom. Therefore, σ-bond formation between the phenolic hydroxy group and the boron complex followed by coordination of the allylic oxygen to the boron atom gives the five-membered cyclic complex. This model can explain the direction of the observed enantioselectivities. The *Re* site of the benzene ring of the substrate is likely shielded by one tolyl group of the sulfonamide ligand. Therefore, the allylic moiety should approach on the *Si* face, giving rise to the (*S*)-alcohol **3**.

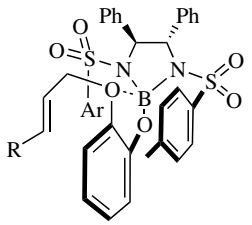
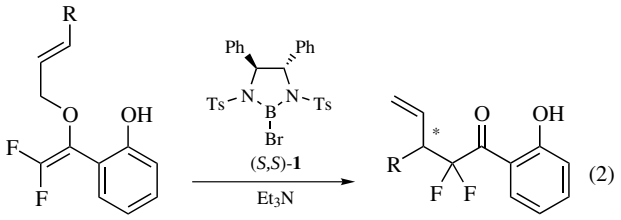


Figure 1

Difluorovinyl allyl ethers can be similarly rearranged.[4] The preparation of β-substituted, α,α-difluorocarbonyl compounds (**5**) is possible upon treatment of **4** with 1.5 equiv of (*S,S*)-**1** in the presence of 1.5 equiv of Et_3N in CH_2Cl_2 at –78 °C, and then stirring at ambient temperature (eq 2).



(**4**) (**5**) (2)

39–90% yield
41–85% ee

Olefin geometry (*E* or *Z*) and steric bulkiness of the R substituent at the *Y*-position of **4** affect reaction temperature requirements and enantioselectivity. In the case of a *Z*-olefin bearing a bulky TMS group in the *Y*-position, the rearrangement proceeds at –78 °C and affords the product in 85% ee. With less bulky substituents on the olefin (both *E* and *Z*), higher reaction temperatures are required leading to a decrease in the enantiomeric excesses.

A postulated six-membered intermediate (Figure 2), formed by the attachment of the chiral boron reagent **1** to the phenolic hydroxy group, and the subsequent coordination of the ethereal oxygen to the boron atom can be used to explain the stereochemical outcome of the rearrangement. The *Si* face of the difluorovinyl ether moiety is shielded by the tolylsulfonyl groups; thus, the allylic moiety approaches preferably from the *Re* face to avoid steric interaction with the aromatic group in the chair-like transition state.

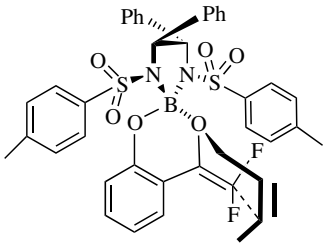
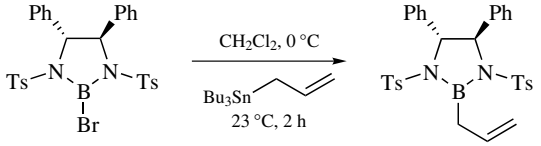


Figure 2

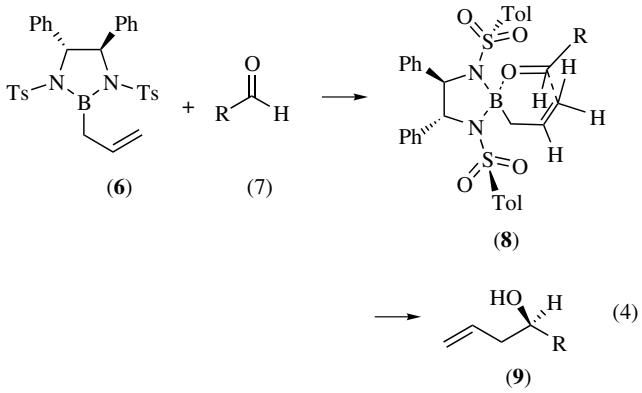
Allylation of Aldehydes. Bromoborane (*R,R*)-**1** reacts with allyltributylstannane to afford the chiral allylborane[2] **6** shown in eq 3.



(*R,R*)-(**1**) (**6**) (3)

Allylborane species **6** reacts with a variety of aldehydes to generate the corresponding homoallylic alcohol **9** in optical

purities ranging from 90 to 98% ee (eq 4). Following the reaction, recovery of the (*R,R*)-bis-*p*-toluenesulfonamide can be achieved by precipitation upon the addition of Et_2O.

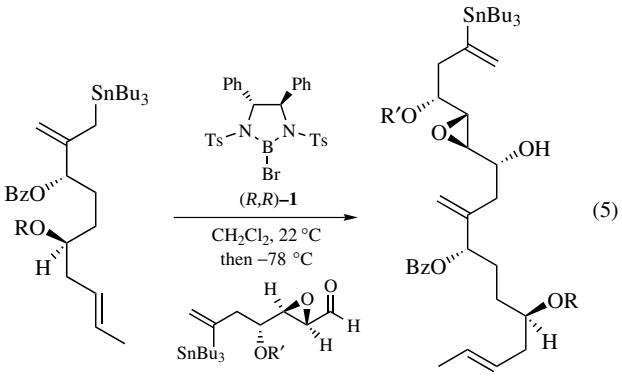


(**6**) (7) (**8**) (**9**) (4)

The observed enantioselectivities can be predicted on the basis of a chair-like transition structure that optimizes stereoelectronic interactions and minimizes steric repulsion between appendages on the five-membered ring, as shown in intermediate **8**.

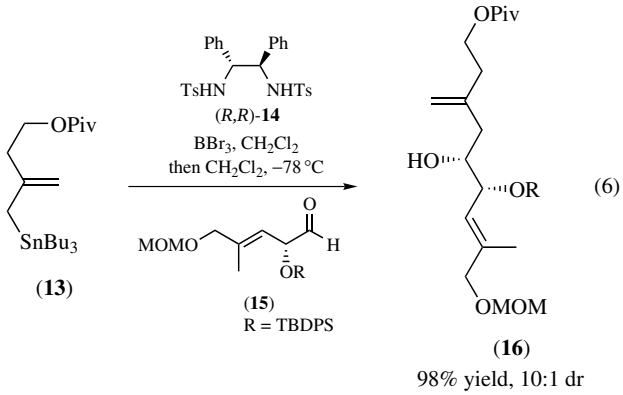
Chiral aldehydes react with the allylborane reagent, affording homoallylic aldehydes in high stereoselectivity, via a putative chair-like transition structure. Substituted allyl groups, including 2-haloallyl groups, can also be used to produce a wide array of products.

This allylation protocol was used in the total synthesis of amphidinolide K.[5–7] to give homoallylic alcohol **12** in 72% yield and 17:1 dr (eq 5). Initial transmetallation of stannane **10** with (*R,R*)-**1** via allylic transposition yielded an intermediate borane. Introduction of aldehyde **11** at –78 °C provided for a facile condensation reaction leading to **12**. Stereocontrol was induced from the 1,2-diphenylethane sulfonamide auxiliary and could be predicted from a Zimmerman–Traxler model with minimized steric repulsions. The high level of selectivity obtained in this case was a result of a matched diastereomeric transition state featuring the inherent Felkin–Ahn selectivity for nucleophilic attack in aldehyde **11**, with the (*S*)-configuration of the benzoate of **10**, as well as the (*R,R*)-antipode of auxiliary **1**, resulting in threefold stereodifferentiation.



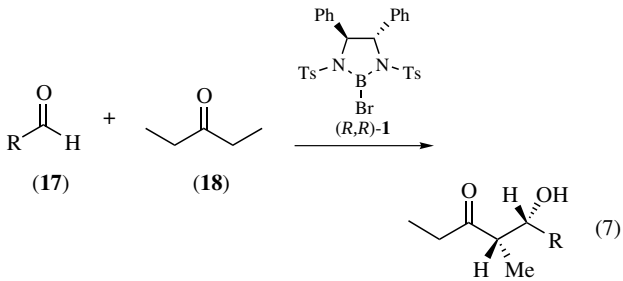
(**10**) R = TBS (**11**) R′ = TIPS (**12**) R = TBS, R′ = TIPS 72% yield, 17:1 dr (5)

The bromoborane can also be prepared in situ. This was shown in synthetic studies toward phorboxazole A (eq 6),[8] where homoallylic alcohol **16** was formed in 98% yield (10:1 dr).



(**13**) (*R,R*)-**14** (**15**) R = TBDPS (**16**) 98% yield, 10:1 dr (6)

Aldol Reactions. *syn*-Aldol adducts can be formed enantioselectively from the reaction of diethyl ketone and various aldehydes using bromoborane (*R,R*)-**1** as a chiral controller (eq 7).[9] Reactions typically proceed in 85–91% yield with > 95% ee. This process led to the highly efficient synthesis of the rice and corn weevil aggregation pheromone sitophilure **19** (R = C_2H_5). Here the bis(tosyl)amide was easily recovered in high yield, since the aldol products were soluble in hexanes, but the chiral backbone was not.[1]



(**17**) (**18**) (*R,R*)-**1** (**19**) 85–95% yield >95% ee (7)

Bromoborane (*R*,R)-**1** can also promote enantioselective aldol coupling between acetate esters or thioesters and aldehydes.[1]

The stereochemistry of the predominating aldol adducts follows the assumption that the phenyl groups of the ligand backbone force the vicinal *N*-sulfonyl substituents to occupy the opposite face of the five-membered ring to which they are attached. The optimum stereoelectronic and steric arrangement of the favored transition structure for the formation of aldol product is shown in Figure 3 and leads to the observed major product **19**.

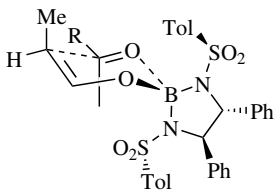
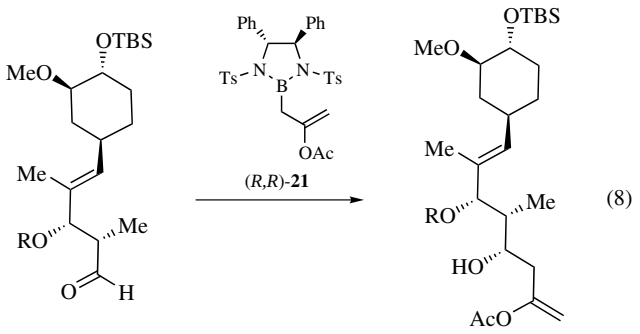


Figure 3

The aldol methodology was applied to the synthesis of FK-506.[7] Treatment of aldehyde **20** with cyclic borane **21** afforded homoallylic alcohol **22** in 17:1 diastereoselectivity (eq 8). Borane **21** was prepared from the reaction of (*S*,*S*)-**1** with 2-acetoxyallyltri-*n*-butylstannane in CH_2Cl_2 for 5 min at –78 °C, and then at 23 °C for 1.5 h. Reaction of the CH_2Cl_2 solution in situ with aldehyde **20** at –78 °C for 1 h produced homoallylic alcohol **22** as the major product. The bis(tosyl)amide from which reagent **21** was derived was efficiently recovered for reuse.

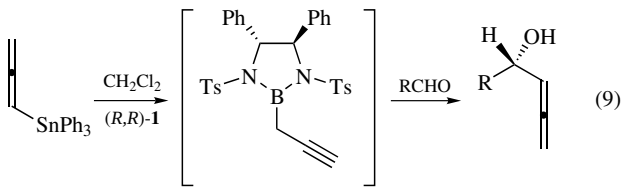


(8)

(**20**)
R = MOM

(**22**)
R = MOM
92% yield, 17:1 dr

Formation of Chiral Propa-1,2-dienyl and Propargyl Alcohols. Reaction of bromoborane (*R*,*R*)-**1** with propadienyltri-*n*-butylstannane **23** in CH_2Cl_2 at 0 °C for 4 h and 23 °C for 0.5 h produced the propargylborane derivative **24**, which reacts in situ with various aldehydes.[10] These reactions (eq 9) produce chiral propa-1,2-dienyl carbinols (**25**) in 72–82% yield with >99% ee. The products can be isolated with a purity of 98–99%, the impurity being the isomeric propargyl carbinol. In these cases, 90% of the bis-*p*-toluenesulfonamide of 1,2-diphenyl-1,2-diaminomethane (the chiral controller) is recovered. Use of (*S*,*S*)-**1** with the opposite enantiomer proceeded with similar efficiency.



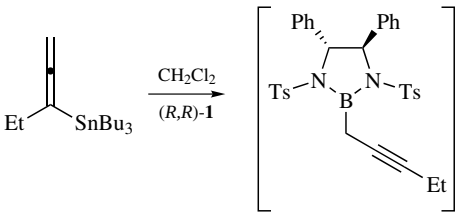
(9)

(**23**) (**24**) (**25**)

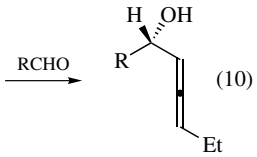
72–82% yield
>99% ee

This method can also be applied to 1,1-disubstituted allenes (**26**) to synthesize **28**, as shown in eq 10.

Derivatives of **1** can be used in the enantioselective propargylation of aldehydes (eq 11). Treatment of 2-propynyltriphenylstannane (**29**) with bromoborane **1** in CH_2Cl_2 at 0 °C for 4 h and 23 °C for 10 min produces allylborane **30**, which reacts with a variety of aldehydes to form propargyl carbinols (**31**). The enantioselection was excellent for the six substrates studied (91–98% ee) and chemical yields ranged from 74 to 81%. In each case, the chiral controller was separated from the propargylic alcohol for reuse by precipitation from 3:1 ether–hexane at 0 °C.



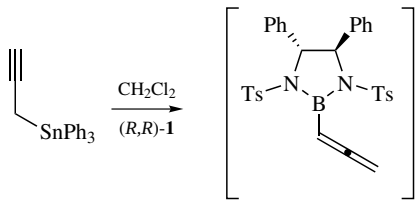
(**26**) (**27**)



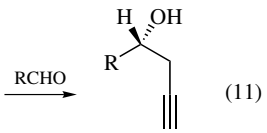
(10)

(**28**)

Attempted Enantioselective Enolborination. Some limitations to the scope of bromoborane **1** in asymmetric processes are documented. For example, attempts to desymmetrize C_s (or C_i) symmetric bifunctional substrates by selective enolborination have not been successful (eq 12).[11]



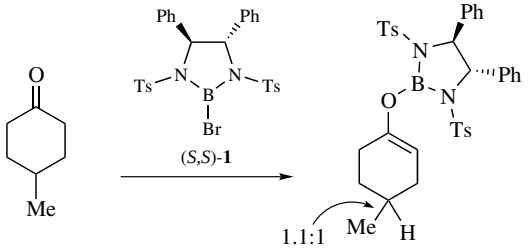
(**29**) (**30**)



(11)

(**31**)

74–81% yield
91–98%ee



(12)

(**32**) (**33**)

First Update

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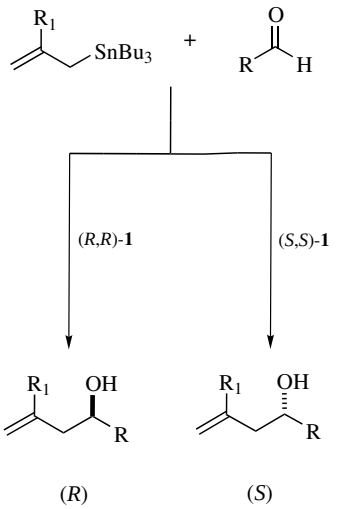
Carbonyl Allylations. Reagent **1** was originally introduced by Corey in 1989 for the asymmetric allylation of aldehydes with tri-*n*-butylallylstannane,[2] as previously reviewed.[1,12] Subsequent studies have demonstrated the utility of this reagent for the stereocontrolled generation of complex homoallylic alcohols via the convergent coupling of various functionalized, C_2-symmetric allylstannanes and substituted aldehydes.[5–8,13–17] The absolute stereochemistry of the newly formed alcohol stereocenter is predictable using a Zimmerman–Traxler model, and product formation is generally governed by the absolute stereochemistry of **1** (eq 13).

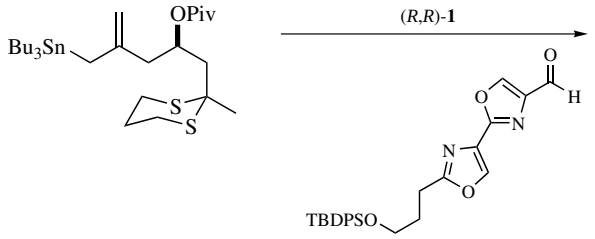


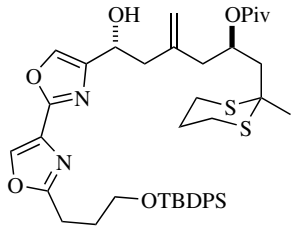
(13)

In situ transmetallation of the starting allylstannane to an intermediate allylic borane is rationalized via a 1,3-transposition pathway. In reactions with chiral aldehydes, matched and mismatched diastereotopic pathways are possible based upon the asymmetry of **1** and the intrinsic face selectivity exhibited for the carbonyl addition process. Yields are generally high (85–99%) with good to excellent stereoselectivity. Numerous functional groups are tolerated in the starting allylstannane, including esters, silyl and benzyl or *para*-methoxybenzyl ethers, dithioketals, and vinylstannanes. Lewis acid-sensitive functionalities (acetals, ketals, tetrahydropyranyl ethers) are not compatible. The aldehyde component may contain a wide variety of common protecting groups and additional functionality, including basic heteroaromatic systems such as pyridines and oxazoles.

Reactions of achiral aldehydes and homochiral stannanes exhibit stereoselectivity, which is predominantly dictated by the chiral auxiliary **1** if the preexisting asymmetry of the stannane is located at least two carbons or more (β) from the reactive allyl unit (eqs 14–16).[5,6]

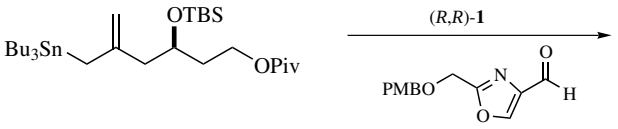
Achiral stannanes undergo reactions with aldehydes bearing α-asymmetry and provide examples of matched diastereoselectivity with respect to **1** (eq 17),[8] as well as cases of mismatched diastereoselection of these controlling factors (eq 18).[5]

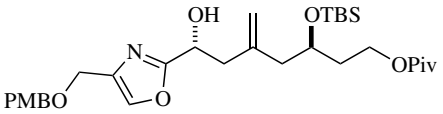




(14)

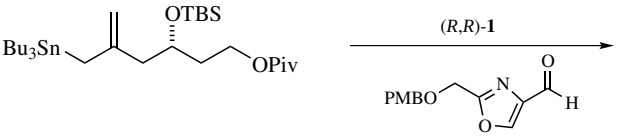
95%, 10.5:1 dr

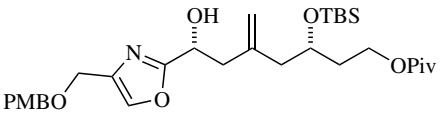




(15)

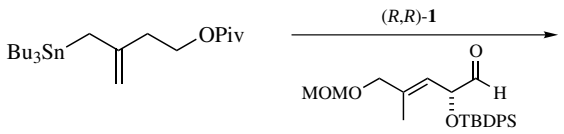
92%, ≥20:1 dr

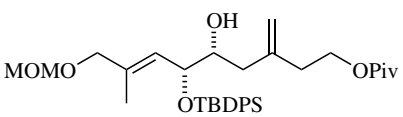




(16)

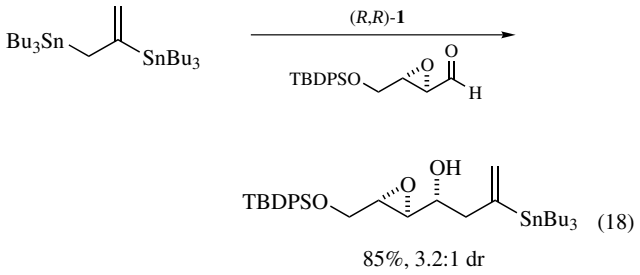
98%, ≥20:1 dr





(17)

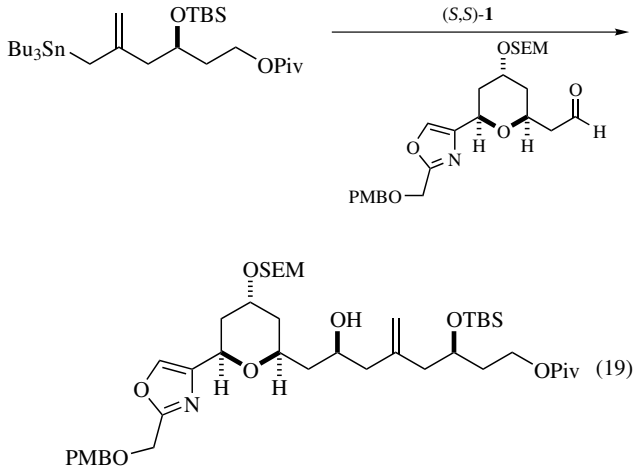
98%, 10:1 dr



(18)

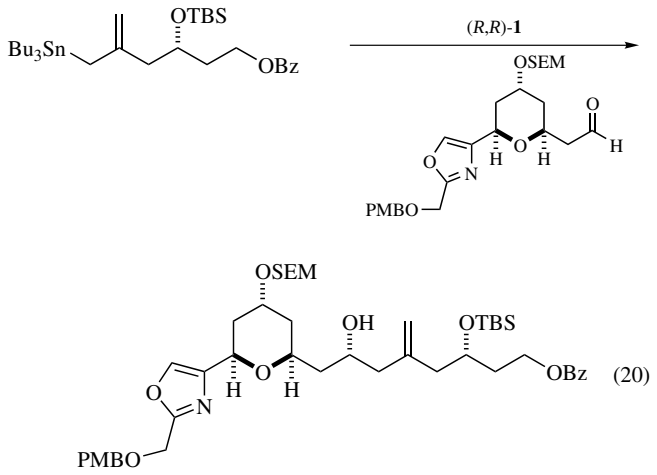
85%, 3.2:1 dr

In a similar fashion, asymmetric allylations with **1** and chiral aldehydes bearing β-substitution also display the expected behavior of diastereotopic transition states (eqs 19 and 20).[5]



(19)

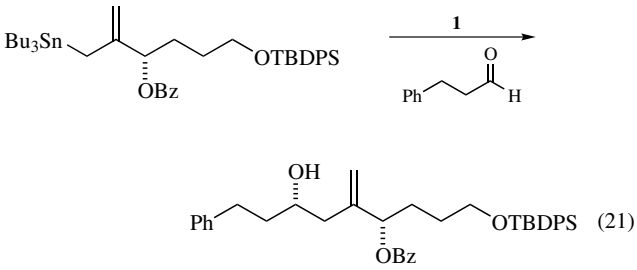
99%, 11.4:1 dr



(20)

88%, 4:1 dr

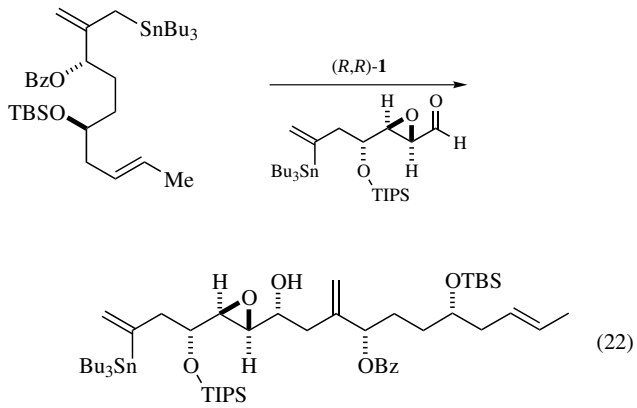
The presence of α-asymmetry in the stannane component can have a dramatic impact on diastereoselection (eq 21).[5] The minimization of $A^{1,3}$ strain in the allylic component is a factor that influences the face selectivity enforced by the auxiliary **1**.



(21)

(*R*,*R*)-**1**: 96%, ≥20:1 dr
(*S*,*S*)-**1**: 94%, 1:1 dr

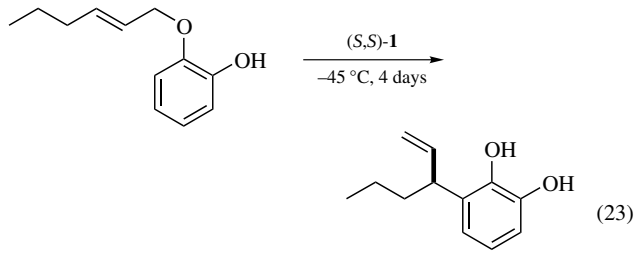
In complex examples, high levels of stereodifferentiation require the consideration of the conjoined influences of α-asymmetry in the allylstannane and chirality of the starting aldehyde, in addition to the choice of auxiliary **1** (eq 22).[4,8]



(22)

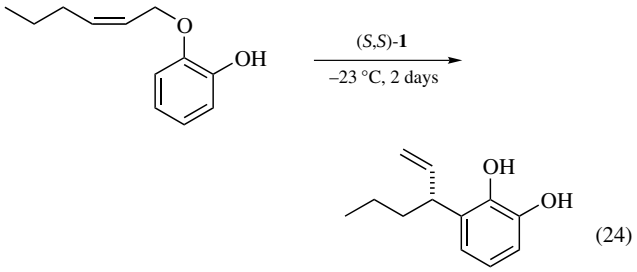
72%, 17:1 dr

Claisen Rearrangements. Claisen rearrangements of catechol allylic ethers, which avoid production of the 'abnormal' Claisen product, have been achieved using 1.5 equiv **1** and 1.5 equiv Et_3N at low temperature in dichloromethane with excellent (80–97%) yields and high (86–95%) enantioselectivities (eqs 23 and 24). The absolute configuration of the newly created benzylic stereocenter is dependent upon both the olefin geometry and the configuration of the controller. Lewis acid catalysis with (*S*,*S*)-**1** and *E*-olefins led to vinylic substituents bearing the *S*-configuration (eq 23), whereas (*S*,*S*)-**1** and *Z*-olefins yielded products with *R*-stereochemistry (eq 24).[3]



(23)

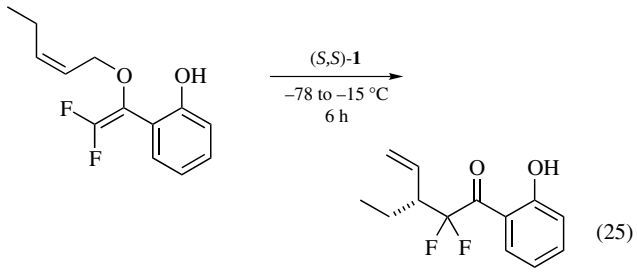
89%, 94% ee



(24)

92%, 95% ee

Similarly, Claisen rearrangements of difluorovinyl allyl ethers occurred with moderate to excellent yields (39–90%) and moderate enantioselectivities (eq 25). Simple alkyl-substituted olefins rearrange at –15 °C with modest stereocontrol (41–56% ee) whereas vinylsilanes rearrange at –78 °C with good (85% ee) selectivity. The absolute configuration of the newly formed benzylic stereocenter appears to depend upon both the geometry (*E* or *Z*) of the starting olefin and the configuration of (**1**), although the absolute stereochemistry of the product was proven only in the case cited below.[4]



(25)

58%, 43% ee

Other Uses. Reagent **1** has been used for enantioselective enolborination, albeit with poor (1.1:1) selectivity.[14] Similar bis-sulfonamide-derived boron Lewis acids have been used for aldol additions,[18–24] ester-Mannich reactions,[25] Diels–Alder reactions,[1,26,27] Ireland–Claisen reactions,[28,29] and [2,3]-Wittig rearrangements.[30,31] Similar bis-sulfonamide-derived aluminum Lewis acids have been used for aldol additions,[1] Diels–Alder reactions,[1,32–35] [2 + 2] ketene–aldehyde cycloadditions,[36,37] cyclopropanation of allylic alcohols,[38–40] and polymerization.[41,42]

Related Reagents. Trifluorosulfonyl; *p*-Fluorophenylsulfonyl; Naphthylsulfonyl; Methylsulfonyl; phenylsulfonyl; 3,5-Bis(trifluoromethyl)phenylsulfonyl; *p*-Nitrosulfonyl Derivatives; Boron–bis-sulfonamide Lewis acids: (*R*,*R*)-1,3-Bis{[3,5-bis(trifluoromethyl) phenyl]sulfonyl}-2-bromo-4,5-diphenyl-1,3,2-diazaborolidine; (*R*, *R*)-1,3-Bis(methylsulfonyl)-2-bromo-4,5-diphenyl-1,3,2-diazabo rolidine; (*R*,*R*)-1,3-Bis[(trifluoromethyl)sulfonyl]-2-bromo 4,5-diphenyl-1,3,2-diazaborolidine; (*R*,*R*)-1,3-Bis(phenylsulfonyl)-2-bromo-4,5-diphenyl-1,3,2-diazaborolidine; (*R*,*R*)-1,3-Bis [(4-fluorophenyl)sulfonyl]-2-bromo-4,5-diphenyl-1,3,2-diazaborolidine; (*R*,*R*)-1,3-Bis[(4-nitrophenyl)sulfonyl]-2-bromo-4,5-diphenyl-1,3,2-diazaborolidine; (*R*,*R*)-1,3-Bis(2-naphthalenylsulfonyl)-2-bromo-4,5-diphenyl-1,3,2-diazaborolidine; (*R*,*R*)-1,3-bis(phenylsulfonyl)-2-bromooctahydro-1*H*-1,3,2-benzodiazaborole; (*R*, *R*)-1,3-bis-[(4-methylphenyl)sulfonyl]-2-bromooctahydro-1*H*-1,3,2-benzodiazaborole.

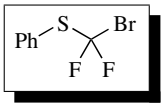
Aluminum–Bis-sulfonamide Lewis Acids: (*R*,*R*)-[*N*,*N*′(1,2-Diphenyl-1,2-ethanediyl)bis(1,1,1-trifluoromethanesulfonamidato)](2-)-*N*,*N*′-methylaluminum; (*R*,*R*)-{[*N*,*N*′-(1,2-Diphenyl-1,2-ethanediyl)bis(1,1,1-trifluoromethanesulfonamidato)]-(2-)-*N*,*N*′}(2-methylpropyl)aluminum; (*R*, *R*)-{[*N*,*N*′-(1,2-diphenyl-1,2-ethanediyl)bis(4-methylbenzenesulfonamidato)](2-)-*N*,*N*′}chloroaluminum; (*R*,*R*)-{[*N*,*N*′-(1,2-Diphenyl-1,2-ethanediyl)bis[3,5-bis(trifluoromethyl)benzenesulfonamidato]](2-)-*N*,*N*′}ethylaluminum; (*S*,*S*)-[*N*,*N*′-(1,2-Diphenyl-1,2-ethanediyl)bis[2,4,6-trimethylbenzenesulfonamidato](2-)-*N*,*N*′]methylaluminum; (*S*,*S*)-[*N*,*N*′-(1,2-Diphenyl-1,2-Ethanediyl) (2,4,6-trimethylbenzenesulfonamidato)-2,4,6-tris(1-methylethyl)benzenesulfonamidato(2-)-*N*,*N*′]methylaluminum; (*S*,*S*)-{[*N*,*N*′-(1,2-Diphenyl-1,2-ethanediyl)bis[4-(1,1-dimethylethyl)-2,6-dimethylbenzenesulfonamidato]](2-)-*N*,*N*′}methylaluminum; (*S*,*S*)-{*N*,*N*′-(1,2-Diphenyl-1,2-ethanediyl)[(4-(1,1-dimethylethyl)-2,6-dimethylbenzenesulfonamidato]-2,4,6-tris(1-methylethyl)-benzenesulfonamidato(2-)-*N*,*N*′}methylaluminum; (*R*,*R*){(*N*,*N*′-(1,2-Diphenyl-1,2-ethanediyl)bis[2,4,6-tris(1-methylethyl)benzenesulfonamidato])(2-)-*N*,*N*′}ethylaluminum; (*S*,*S*)-{[*N*,*N*′-[1,2-Bis(3,5-dimethylphenyl)-1,2-ethanediyl]bis(1,1,1-trifluoromethanesulfonamidato)](2-)-*N*,*N*′}-methylaluminum; (*R*,*R*)-{[*N*,*N*′-1,2-Cyclohexanediylbis(1,1,1-trifluoromethanesulfonamidato)](2-)-*N*,*N*′}methylaluminum; (*R*,*R*)-{[*N*,*N*′-1,2-Cyclohexanediylbis(benzenesulfonamidato)](2-)-*N*, *N*′} (2-methylpropyl)aluminum; (*R*,*R*)-{[*N*,*N*′-1,2-Cyclohexanediyl-bis (4-nitrobenzenesulfonamidato)](2-)-*N*,*N*′}methylaluminum; (*R*,*R*)-{[*N*,*N*′-1,2-Cyclohexanediylbis(4-nitrobenzenesulfonamidato)]-(2-)-*N*,*N*′} ethylaluminum; (*R*,*R*)-{[*N*,*N*′-1,2-Cyclohexanediylbis(4-nitrobenzenesulfonamidato)](2-)-*N*,*N*′}(2-methylpropyl)-aluminum; (*R*,*R*)-{(*N*,*N*′-1,2-Cyclohexanediylbis[4-(trifluoromethyl) benzenesulfonamidato])(2-)-*N*,*N*′}(2-methylpropyl)-aluminum; (*R*,*R*){(*N*,-*N*′-1,2-Cyclohexanediylbis[3,5-bis(trifluoromethyl)benzenesulfonamidato])(2-)-*N*,*N*′}(2-methylpropyl)aluminum.

Other chiral controllers for allylation: (*R*)-[(1,1′-Binaphthalene)-2,2′-diolato(2-)-κ*O*,κ*O*′]dichlorotitanium; (*R*)-[(1,1′-Binaphthalene)-2,2′-diolato(2-)-
-κ*O*,κ*O*′]bis(2-propanolato)titanium; (*R*)-[(1,1′-Binaphthalene)-2,2′-diolato(2-)-κ*O*,κ*O*′]bis(2-propanolato) zirconium; (*R*)-[(1,1′-Binaphthalene)-2,2′-diylbis(diphenylphosphine-κ*P*)]trifluoromethanesulfonato-κ*O*-silver; Chloro(η^5-cyclopentadienyl)[(4*R*,*trans*)-2,2-dimethylα,α,α′,α′-tetraphenyl-1,3-dioxo-lane-4,5-dimethanolato(2-)-*O*α, *O*α′]titanium; 2,2-dimethyl-α,α,α′,α′′-tetraphenyl-1,3-Dioxolane-4,5-dimethanolatotitanium diisopropoxide; chloro(cyclopentadienyl)bis[3-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)]titanium; {2,2′-Methylenebis-[(4*S*,5*R*)-4,5-dihydro-4,5-diphenyloxazole-κ*N*3]}bis(trifluoromethanesulfonato-κ*O*-zinc; Aqua{2,6-bis[(4*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl-κ*N*3]phenyl-κ*C*}dichlororhodium; (*S*,*S*) -[2,6-Bis(1-methylethoxy)benzoyl]oxy-5-oxo-,3,2-dioxaborolane-4-acetic Acid; *B*-Methoxydiisopinocampheylborane; 1,3,2-Benzodioxastannol-2-ylidene Complex with Diisopropyl Tartrate; 2,2,2-Trifluoro-*N*-[(1*R*,2*R*)-1-methyl-2-phenyl-2-[(trimethylsilyl)oxy]ethylacetamide; (*R*,*R*)-Octahydro-1,3-dimethyl-2-(1-piperidinyl)-1*H*-1,3,2-benzodiazaphosphole-2-oxide.

1. Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B., *J. Am. Chem. Soc.* **1989**, *111*, 5493.

2. Corey, E. J.; Yu, C.-M.; Kim, S. S., *J. Am. Chem. Soc.* **1989**, *111*, 5495.
3. Ito, H.; Sato, A.; Taguchi, T., *Tetrahedron Lett.* **1997**, *38*, 4815.
4. Ito, H.; Sato, A.; Kobayashi, T.; Taguchi, T., *J. Chem. Commun.* **1998**, 2441.
5. Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Clark, M. P., *Tetrahedron Lett.* **1998**, *39*, 7251.
6. Williams, D. R.; Brooks, D. A.; Berliner, M. A., *J. Am. Chem. Soc.* **1999**, *121*, 4924.
7. Williams, D. R.; Meyer, K. G., *J. Am. Chem. Soc.* **2001**, *123*, 756.
8. Williams, D. R.; Clark, M. P.; Emde, U.; Berliner, M. A., *Org. Lett.* **2000**, *2*, 3023.
9. Corey, E. J.; Huang, H.-C., *Tetrahedron Lett.* **1989**, *30*, 5235.
10. Corey, E. J.; Yu, C.-M.; Lee, D.-H., *J. Am. Chem. Soc.* **1990**, *112*, 878.
11. Ward, D. E.; Lu, W.-L., *J. Am. Chem. Soc.* **1998**, *120*, 1098.
12. Gage, J. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995, Vol. 4, p 2207.
13. Williams, D. R.; Clark, M. P.; Berliner, M. A., *Tetrahedron Lett.* **1999**, *40*, 2287.
14. Ward, D. E.; Lu, W.-L., *J. Am. Chem. Soc.* **1998**, *120*, 1098.
15. Pikul, S.; Corey, E., *J. Org. Synth.* **1993**, *71*, 22.
16. Wang, S.-M.; Sharpless, B. A., *J. Org. Chem.* **1994**, *59*, 8302.
17. Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P., *Synthesis* **1990**, 1023.
18. Corey, E. J.; Kim, S. S., *J. Am. Chem. Soc.* **1990**, *112*, 4976.
19. Corey, E. J.; Kim, S. S., *Tetrahedron Lett.* **1990**, *31*, 3715.
20. Corey, E. J.; Soongyu, C., *Tetrahedron Lett.* **1991**, *32*, 2857.
21. Corey, E. J.; Lee, D.-H.; Soongyu, C., *Tetrahedron Lett.* **1992**, *33*, 6735.
22. Corey, E. J.; Lee, D.-H., *Tetrahedron Lett.* **1993**, *34*, 1737.
23. Corey, E. J.; Soongyu, C., *Tetrahedron Lett.* **2000**, *41*, 2765.
24. Corey, E. J.; Soongyu, C., *Tetrahedron Lett.* **2000**, *41*, 2769.
25. Corey, E. J.; Decicco, C. P.; Newbold, R. C., *Tetrahedron Lett.* **1991**, *32*, 5287.
26. Bienayme, H.; Longeau, A., *Tetrahedron* **1997**, *53*, 9637.
27. Richardson, B. M.; Day, C. S.; Welker, M. E., *J. Organomet. Chem.* **1999**, *577*, 120.
28. Corey, E. J.; Lee, D.-H., *J. Am. Chem. Soc.* **1991**, *113*, 4026.
29. Corey, E. J.; Roberts, B. E.; Dixon, B. R., *J. Am. Chem. Soc.* **1995**, *117*, 193.
30. Fujimoto, K.; Nakai, T., *Tetrahedron Lett.* **1994**, *35*, 5019.
31. Fujimoto, K.; Matsuhashi, C.; Nakai, T., *Heterocycles* **1996**, *42*, 423.
32. Corey, E. J.; Imai, N.; Pikul, S., *Tetrahedron Lett.* **1991**, *32*, 7517.
33. Corey, E. J.; Sarchar, S.; Bordner, J., *J. Am. Chem. Soc.* **1992**, *114*, 7938.
34. Pikul, S.; Corey, E., *J. Org. Synth.* **1993**, *71*, 30.
35. Corey, E. J.; Sarshar, S.; Lee, D.-H., *J. Am. Chem. Soc.* **1994**, *116*, 12089.
36. Dymock, B. W.; Kocienski, P. J.; Pons, J.-M., *J. Chem. Soc., Chem. Commun.* **1996**, 1053.
37. Miyano, S.; Hattori, T.; Uesugi, S.; Tamai, Y.; Sayo, N., *Jpn. Kokai Tokkyo Koho* (131:228639) **1999**.
38. Imai, N.; Takahashi, H.; Kobayashi, S., *Chem. Lett.* **1994**, 177.
39. Kobayashi, S.; Imai, N.; Takahashi, H., *Jpn. Kokai Tokkyo Koho* (CAN 123:169276) **1995**.
40. Kobayashi, S.; Imai, N.; Takahashi, H., *Jpn. Kokai Tokkyo Koho* (CAN 124:146482) **1995**.
41. Itsuno, S.; Tada, S.; Ito, K., *Chem. Commun.* **1997**, 933.
42. Kamahori, K.; Tada, S.; Ito, K.; Itsuno, S., *Macromolecules* **1999**, *32*, 541.

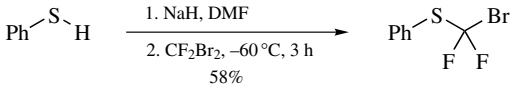
Bromodifluorophenylsulfanylmethane



[78031-08-0] $C_7H_5BrF_2S$ (MW 239.09)
InChI = 1/C7H5BrF2S/c8-7(9,10)11-6-4-2-1-3-5-6/h1-5H
InChIKey = HXZWRRXLBDCJMB-UHFFFAOYAY

(bromodifluoromethyl phenyl sulfoxide and sulfone precursors; [difluoro(phenylsulfanyl)methyl]trimethylsilane precursor; *gem*-difluoromethylene (CF_2) building block; α-arylsulfanyl-α-fluoro carbenoid; difluoro(phenylsulfanyl)-methyl ($PhSCF_2$) building block; *gem*-difluoromethylenation)

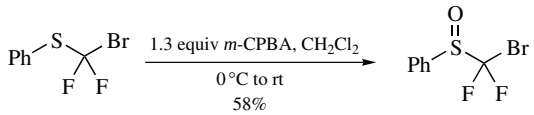
Physical Data: bp 97 °C/34 mmHg; bp 62–64 °C/2 mmHg.
Solubility: soluble in most organic solvents.
Preparative Methods: several methods are available.[1] The most convenient is the reaction of thiophenol with dibromodifluoromethane using sodium hydride as the base in DMF (eq 1).[1a]



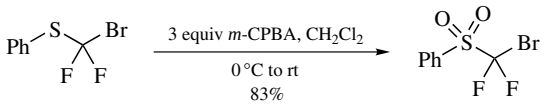
(1)

Handling, Storage, and Precautions: the material should be handled in a well-ventilated fume hood and can be kept cooled in the refrigerator for months without any appreciable decomposition.

Oxidation to Sulfoxide and Sulfone. Bromodifluorophenylsulfanylmethane can be oxidized to bromodifluoromethyl phenyl sulfoxide and bromodifluoromethyl phenyl sulfone by 1 and 2 equiv of *m*-chloroperbenzoic acid, respectively (eqs 2 and 3).[1b]



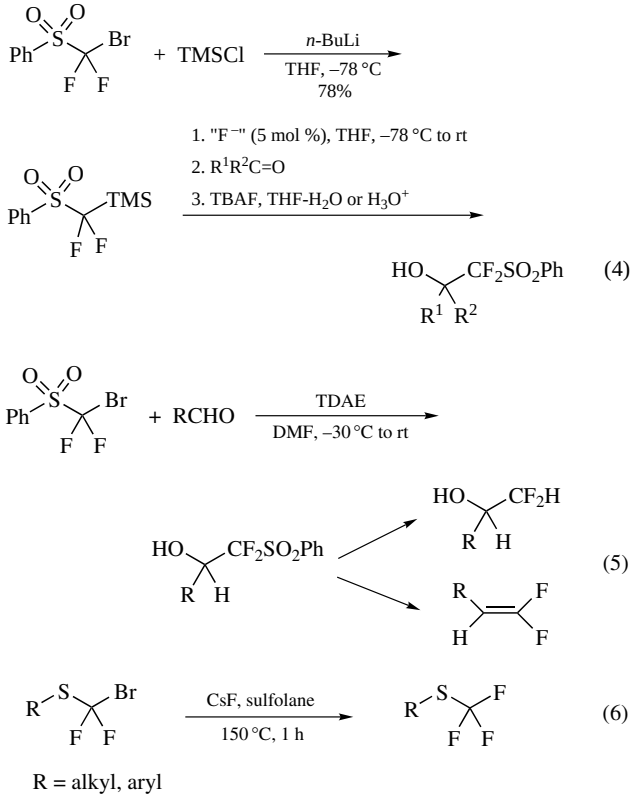
(2)



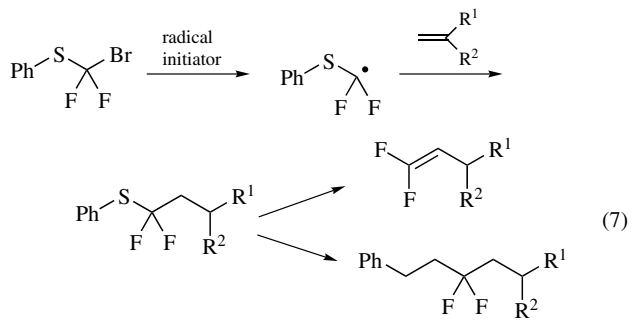
(3)

Bromodifluoromethyl phenyl sulfone can be transformed to [difluoro(phenylsulfonyl)methyl]trimethylsilane which was employed for fluoride-induced (phenylsulfonyl)difluoromethylation (eq 4).[2] Alternatively, the reaction of bromodifluoromethyl phenyl sulfone with aldehydes mediated by electron-transfer reagent, tetrakis(dimethylamino)ethylene (TDAE), yields (phenylsulfonyl)-difluoromethylated alcohols in good yields which can be further transformed to difluoromethyl alcohols and *gem*-difluoroalkenes via reductive desulfonylation and Julia olefination, respectively (eq 5).[3]

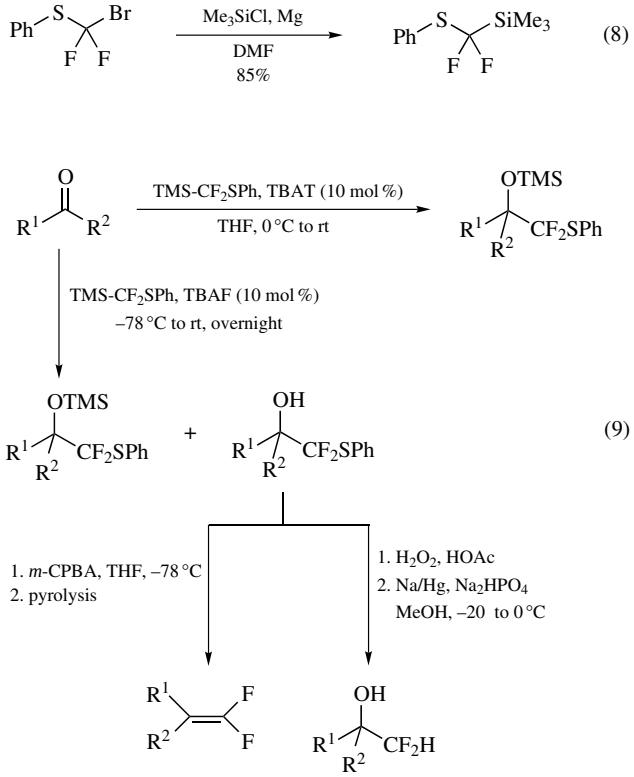
Trifluoromethyl Phenyl Sulfide. The reaction of bromodifluorophenylsulfanylmethane with cesium fluoride (CsF) in sulfolane gives trifluoromethyl phenyl sulfide in moderate yield (eq 6).[4]



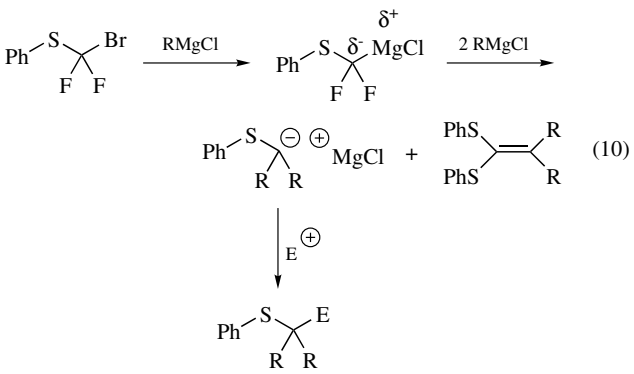
***gem*-Difluoromethylene Building Block.** The bromodifluorophenylsulfanylmethane has been demonstrated being the *gem*-difluoromethylene building block for the synthesis of *gem*-difluoroalkanes containing a midchain CF_2 moiety and *gem*-difluoroalkenes via the reaction of difluoro(phenylsulfanyl) methyl radical with olefins (eq 7).[5]



[Difluoro(phenylsulfanyl)methyl]trimethylsilane (TMS–CF_2–SPh). The Barbier coupling reaction of bromodifluorophenylsulfanylmethane, magnesium metal, and chlorotrimethylsilane affords difluoro(phenylsulfanyl)methyl]trimethylsilane in good yield (eq 8).[6] The fluoride-induced nucleophilic difluoro(phenylsulfanyl)methylation reaction of aldehydes and ketones with TMS–CF_2–SPh gives the corresponding adducts, i.e., silyl ethers and carbinols, depending on the type of fluoride source employed (eq 9).[6,7] The phenylsulfanyl moiety can be removed by oxidation– desulfonylation.[6b] In addition, subsequent oxidation of the carbinol sulfide to sulfoxide followed by vacuum pyrolysis gives the corresponding *gem*-difluoroalkenes.[7]



α-Phenylsulfanyl-α-fluoro Carbenoid. The reaction of bromodifluorophenylsulfanylmethane with Grignard reagents, which upon trapping with electrophiles gives alkyl phenyl sulfide and ketene dithioacetal. The reaction is proposed to proceed via a novel α-phenylsulfanyl-α-fluoro carbenoid (eq 10).[8]



1. (a) Suda, M.; Hino, C., *Tetrahedron Lett.* **1981**, *22*, 1997. (b) Burton, D. J.; Wiemers, D. M., *J. Fluorine Chem.* **1981**, *18*, 573. (c) Rico, I.; Wakselman, C., *Tetrahedron Lett.* **1981**, *22*, 323. (d) Rico, I.; Wakselman, C., *Tetrahedron* **1981**, *37*, 4209. (e) Li, X.; Jiang, X.; Gong, Y.; Pan, H., *Huaxue Xuebao* **1985**, *43*, 260.
2. Ni, C.; Hu, J., *Tetrahedron Lett.* **2005**, *46*, 8273.
3. Prakash, G. K. S.; Wang, Y.; Hu, J.; Olah, G. A., *J. Fluorine Chem.* **2005**, *126*, 1361.
4. Jpn. Kokai Tokkyo Koho Pat. JP 57 080 329 A2 19 820 519 Showa; CAN 97:144354 (1982).
5. Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M., *J. Org. Chem.* **2004**, *69*, 6913.

6. (a) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A., *J. Org. Chem.* **2003**, *68*, 4457. (b) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A., *J. Fluorine Chem.* **2005**, *126*, 529.
7. Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V., *Tetrahedron* **2006**, *62*, 5973.
8. Pohmakotr, M.; Ieawsuwan, W.; Tuchinda, P.; Kongsaeree, P.; Prabpai, S.; Reutrakul, V., *Org. Lett.* **2004**, *6*, 4547.

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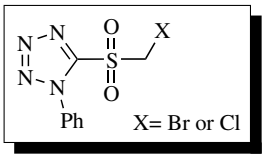
Bromomethanesulfonyl Phenyl Tetrazole[1] (Chloro)

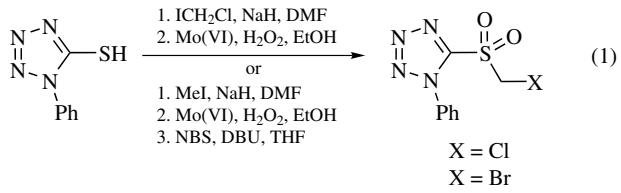


[880634-13-9] $C_8H_7BrN_4O_2S$ (MW 303.14)
InChI = 1/C8H7BrN4O2S/c9-6-16(14,15)8-10-11-12-13(8)7-4-2-1-3-5-7/h1-5H,6H2
InChIKey = ISANWZWXGFFOHT-UHFFFAOYAE
[880634-12-8] $C_8H_7ClN_4O_2S$ (MW 258.68)
InChI = 1/C8H7ClN4O2S/c9-6-16(14,15)8-10-11-12-13(8)7-4-2-1-3-5-7/h1-5H,6H2
InChIKey = BDGWHTJFPWNLBE-UHFFFAOYAH

Physical Data: mp 73.3–73.5 °C (bromo); HRMS $(M+H)^+$ calc: 302.9552, found: 302.9550.
mp 63.3–63.5 °C (chloro); HRMS $(M+Na)^+$ calc: 280.9876, found: 280.9884.
Solubility: soluble in organic solvents (toluene, CH_2Cl_2, Et_2O, THF, acetone, DMF, DMSO, MeOH); insoluble in H_2O and hexanes.
Form Supplied in: white solid.
Analysis of Reagent Purity: NMR, HPLC, HRMS.
Handling, Storage, and Precautions: these reagents can be used safely under normal laboratory conditions.

Introduction. These reagents have been used in a modified Julia olefination[2] with a variety of aldehydes to generate alkenyl halides, which are important precursors in many useful organic transformations including the well-known Stille,[3] Suzuki,[4] Heck,[5] and Sonogashira[6] couplings. Alkenyl halides formed in this manner are produced in good yield with high *E*/*Z*-stereoselectivity that is greatly influenced by the nature of the solvent, the temperature, the base, and the additive used.

Syntheses of α-Halomethyl Sulfone Reagents. Syntheses of the starting sulfone reagents were accomplished employing a two- or a three-step process from commercially available reagents (eq 1). Phenyltetrazole was chosen as the desired heterocyclic partner since this group usually gives better *E*/*Z*-stereoselectivity compared to benzothiazole.[7] Simple alkylation with chloroiodomethane or iodomethane, followed by an oxidation of these thioethers with a catalytic amount of ammonium molybdate in the presence of hydrogen peroxide, afforded the desired α-chloromethylsulfone reagent or the methylsulfone. This methylsulfone was then directly brominated in order to access the desired α-bromomethylsulfone reagent.

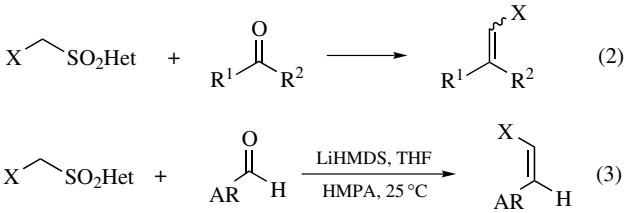


(1)

An alternative chemoselective monohalogenation of β-keto sulfones using potassium halide and hydrogen peroxide could be employed to afford the desired halomethyl sulfone reagents.[8] Furthermore, direct alkylation of sulfinate salts with methylene bromide afforded α-bromosulfones in moderate yields.[9]

Halomethyl sulfone reagents have been used as α-carbanion stabilizing substituents as well as precursors for alkenes, epoxides, and aziridines syntheses.[10] It is worth mentioning that only aromatic substrates were used, typically phenyl sulfones, and no example has been reported with heterocyclic compounds such as phenyltetrazole. In this regard, we will focus on olefination reactions only.

Olefination. These halomethanesulfonyl phenyl tetrazole reagents are competing against other well-known methods to create alkenyl halides. First, the Julia-type olefination, which involves the coupling of these α-halomethyl sulfone reagents with carbonyl precursors, was reinvestigated to generate a large variety of alkenyl halides (eq 2).[11] The best reaction conditions to obtain *Z*-stereoselectivity involved the addition of LiHMDS to a mixture of the aldehyde, the reagent, and HMPA in THF at room temperature (eq 3). This methodology provided alkenyl halides in high yields with excellent stereoselectivity.



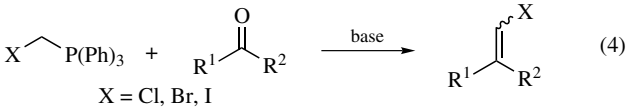
(2)

(3)

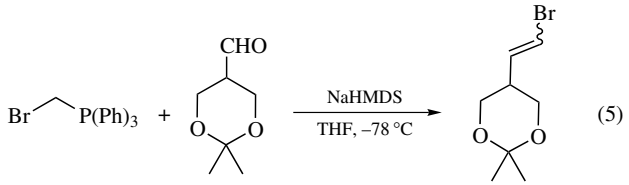
X = Cl, Br

Electronic and steric effects play an important role in this transformation and some limitations have been observed. Also, the scope was limited to electron-rich aldehyde precursors with regards to *E*-alkenyl halide formation, in which the best additive was $MgBr_2/Et_2O$ instead of HMPA.

Secondly, Wittig-type olefination involving α-halomethyltriphenylphosphoranes can afford the desired alkenyl halides in moderate to good yields with good stereoselectivities favoring the *Z*-isomer (eq 4).[12] However, phosphonium salts suffer from tedious preparation and the triphenylphosphine oxide by-product can be hard to remove from the final product. The *E*/*Z*-selectivity can also be poor, as observed in the Cassiol total synthesis (eq 5).[13]



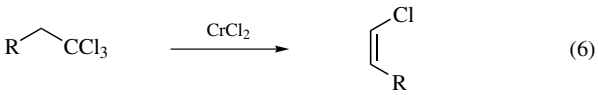
(4)



(5)

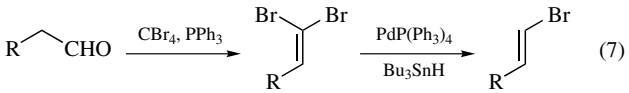
61% yield
E/*Z* (1/1)

Reduction of trichloroalkanes with $CrCl_2$ afforded high *Z*-stereoselectivity of the desired alkenyl chlorides (eq 6).[14] These trichloroalkanes are easily prepared by direct displacement of the corresponding bromide with the anion of chloroform. Of course, this method is limited to the synthesis of alkenyl chlorides.



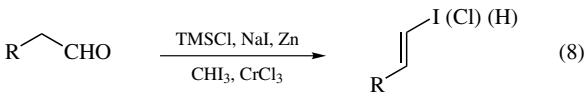
(6)

Corey–Fuchs reaction followed by palladium-catalyzed debromination with Bu_3SnH also gives *Z*-alkenyl bromide selectively (eq 7).[15] This two-step method has been used successfully in many syntheses of natural products like morphine by Trost[15a] and cephalostatin analogues by Tietze.[15b]



(7)

In contrast, Takai methodology provides selectively the *E*-alkenyl halide isomer (eq 8).[16] One drawback of this reaction is the formation of the corresponding alkenyl chlorides and the reduced alkenes, which can be problematic to purify.



(8)

Other syntheses of alkenyl halides have been published over the last decade using different approaches such as selective hydrogenation, hydroboration/protonolysis, metal-catalyzed addition, and E_2 elimination just to name a few.

Conclusion. In conclusion, α-halomethyl sulfone reagents can be efficiently coupled to aldehydes to afford the corresponding alkenyl halides in good yields with excellent *Z*-stereoselectivity using the modified Julia olefination. These reagents are easily prepared from commercially available sources and represent a good alternative to other reagents.

1. Lebrun, M.-E.; Le Marquand, P.; Berthelette, C., *J. Org. Chem.* **2006**, *71*, 2009.
2. (a) Review: Blakemore, P. R., *J. Chem. Soc., Perkin Trans. 1* **2002**, *23*, 2563. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O., *Tetrahedron Lett.* **1991**, *32*, 1175. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O., *Bull. Soc. Chim. Fr.* **1993**, *130*, 856. (d) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O., *Bull. Soc. Chim. Fr.* **1993**, *130*, 336.
3. (a) Stille, J. K., *Angew. Chem.* **1986**, *98*, 504. (b) Stille, J. K., *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Espinet, P.; Echavarren, A. M., *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.
4. Review on Suzuki reactions: Miyaura, N., Suzuki, A., *Chem. Rev.* **1995**, *95*, 2457.
5. (a) Heck, R. F.; Nolley, J. P., *J. Org. Chem.* **1972**, *14*, 2320. (b) Mizoroki, T.; Mori, K.; Ozaki, A., *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (c) Overman, L. E.; Dounay, A. B., *Chem. Rev.* **2003**, *103*, 2945. (d) Beletskaya, I. P.; Cheprakov, A. V., *Chem. Rev.* **2000**, *100*, 3009.
6. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N., *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N., *Synthesis* **1980**, 627. (c) Negishi, E.-i.; Anastasia, L., *Chem. Rev.* **2003**, *103*, 1979. (d) Chinchilla, R.; Najera, C., *Chem. Rev.* **2007**, *107*, 874.
7. Others heterocycles have been used: for BT and PT, see (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A., *Synlett* **1998**, 26. (b) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V., *Synthesis* **1996**, 285. For PYR, see Charette, A. B.; Berthelette, C.; St-Martin, D., *Tetrahedron Lett.* **2001**, *42*, 5149 and 6619. For TBT, see Kocienski, P. J.; Bell, A.; Blakemore, P. R., *Synlett* **2000**, 365.
8. Suryakiran, N.; Prabhakar, P.; Srikanth Reddy, T.; Chinni Mahesh, K.; Rajesh, K.; Venkateswarlu, Y., *Tetrahedron Lett.* **2007**, *48*, 877. (b) Suryakiran, N.; Srikanth Reddy, T.; Suresh, V.; Lakshman, M.; Venkateswarlu, Y., *Tetrahedron Lett.* **2006**, *47*, 4319.
9. Ziegler, W. M.; Connor, R., *J. Am. Chem. Soc.* **1940**, *62*, 2596.
10. (a) Jonczyk, A.; Banko, K.; Makosza, M., *J. Org. Chem.* **1975**, *40*, 266. (b) Bordwell, F. G.; Cooper, G. D., *J. Am. Chem. Soc.* **1951**, *73*, 5184. (c) Arai, S.; Ishida, T.; Shioiri, T., *Tetrahedron Lett.* **1998**, *39*, 8299. (d) Adamczyk, M.; Dolence, E. K.; Watt, D. S.; Christy, M. R.; Reibenspies, J. H.; Anderson, O. P., *J. Org. Chem.* **1984**, *49*, 1378. (e) Dolence, E. K.; Adamczyk, M.; Watt, D. S.; Rasell, G. B.; Horn, D. H. S., *Tetrahedron Lett.* **1985**, *26*, 1189. (f) Arai, S.; Ishidu, T.; Shioiri, T., *Tetrahedron Lett.* **1998**, *39*, 8299. (g) Reutrakul, V.; Prapansiri, V.; Panyachotipun, C., *Tetrahedron Lett.* **1984**, *25*, 1949. (h) Trost, B. M. In *Comprehensive Organic Chemistry*; Pergamon Press: 1993; Vol. 1, p 530.
11. (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O., *Tetrahedron Lett.* **1991**, *32*, 1175. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O., *Bull. Soc. Chim. Fr.* **1993**, *130*, 856. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O., *Bull. Soc. Chim. Fr.* **1993**, *130*, 336.
12. (a) Stork, G.; Zhao, K., *Tetrahedron Lett.* **1989**, *30*, 2173. (b) Seyferth, D.; Heeren, J. K.; Singh, G.; Grim, S. O.; Hughes, W. B., *J. Organomet. Chem.* **1966**, *5*, 267. (c) Matsumoto, M.; Kuroda, K., *Tetrahedron Lett.* **1980**, *21*, 4021.
13. Taber, D. F.; Meagley, R. P.; Doren, D. J., *J. Org. Chem.* **1996**, *61*, 5723.
14. Baati, R.; Barma, D. K.; Krishna, U. M.; Mioskowski, C.; Falck, J. R., *Tetrahedron Lett.* **2002**, *43*, 959.
15. (a) Trost, B. M.; Tang, W.; Toste, F. D., *J. Am. Chem. Soc.* **2005**, *127*, 14785. (b) Tietze, L. F.; Krahnert, W.-R., *Chem. Eur. J.* **2002**, *8*, 2116. (c) Hayford, A.; Kaloko, J. Jr.; El-Kazaz, S.; Bass, G.; Harrison, C.; Corprew, T., *Org. Lett.* **2005**, *7*, 2671.
16. (a) Takai, K.; Nitta, K.; Utimoto, K., *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Takai, K.; Ichiguchi, T.; Hikasa, S., *Synlett* **1999**, *8*, 1268.

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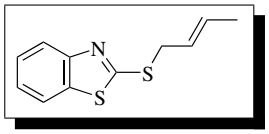
Merck Frosst Centre for Therapeutic Research, Montréal, Québec, Canada

2-(2-Butenylthio)benzothiazole



[89805-98-1] $C_{11}H_{11}NS_2$ (MW 221.37)

InChI = 1/C11H11NS2/c1-2-3-8-13-11-12-9-6-4-5-7-10(9)14-11/h2-7H,8H2,1H3

InChIKey = XUMHHDLGNBREGC-UHFFFAOYAP

(allylic electrophile which allows efficient control of the chemo-,[1] regio-, and stereoselectivity[2,3] in the C–C coupling process by reaction with organocopper reagents)

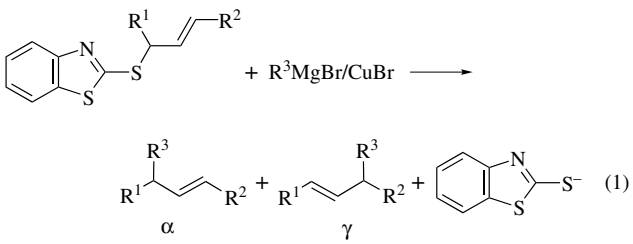
Solubility: sol all solvents except water.

Form Supplied in: white oils or solids; not commercially available.

Preparative Methods: 2-allyloxybenzothiazoles are prepared by reaction of potassium allyloxides with 2-chlorobenzothiazole in dry ether at rt.[2] 2-Allylthiobenzothiazoles are prepared by reaction of allylic alcohols with 2,2′-dithiobis(benzothiazole) and triphenylphosphine or with benzothiazole-2-thiol, diethyl azodicarboxylate, and triphenylphosphine in dry toluene at rt.[3]

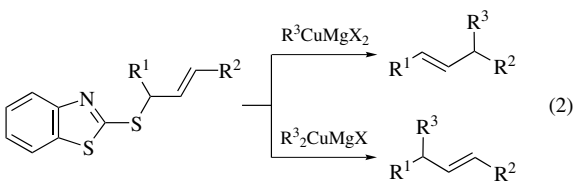
Handling, Storage, and Precautions: store at 5 °C. Safety and handling data not available.

2-Allylthiobenzothiazoles. The reaction of these substrates with organocopper reagents, prepared by reaction of Grignard reagents with copper(I) bromide, leads to C–C coupling products (eq 1).

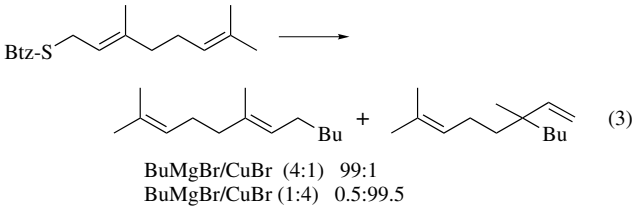


(1)

Efficient regiocontrol of this process (α- or γ-substitution) depends on the nature of the organometallic reagent. High ratios of RMgX:CuX, which favor the formation of organocuprates, give only α-substituted products, whereas lower ratios, which favor the formation of organocopper reagents RCu, afford exclusively γ-substituted products (eq 2).[3] γ-Substitution occurs independently of the steric hindrance of the R^2 group in the allylic sulfide (eq 3).



(2)

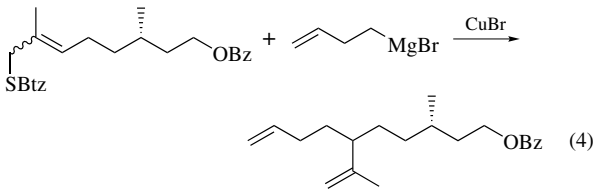


(3)

BuMgBr/CuBr (4:1) 99:1

BuMgBr/CuBr (1:4) 0.5:99.5

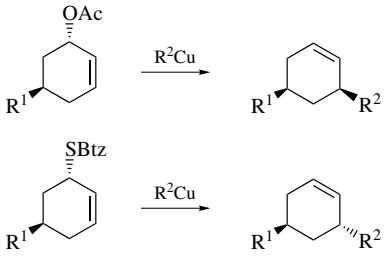
These features have been applied to a simple synthesis of California red scale pheromone[4] starting from the benzothiazole sulfide/benzyl ether of (*S*)-(−)-citronellol (eq 4).



(4)

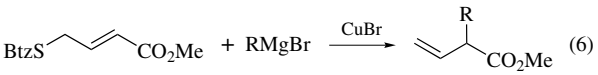
Btz = benzothiazol-2-yl

Stereodivergent pathways relative to other allylic systems (e.g. allylic acetates)[5] have been found[6] in the reactions of cyclic allylic sulfides or ethers of benzothiazole with organocopper reagents. In this case the S_N2' process occurs with *syn* stereochemistry (eq 5) and is due to the anchimeric coordination of the organometallic reagent with the heterocyclic moiety. This has been utilized for regio- and stereocontrolled access to branched-chain sugars.



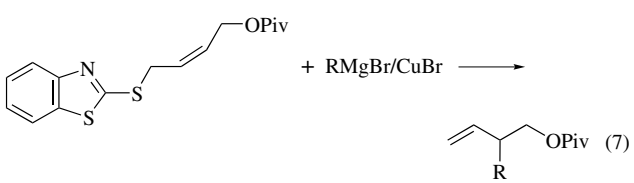
(5)

The importance of coordination in dictating the stereo- and regioselectivity is further demonstrated[7] by the reactions of α,β-enoates γ-substituted by a *S*-benzothiazolyl group with organocopper reagents to give, in a anti-Michael fashion, α-alkylated-β,γ-enoates (eq 6).



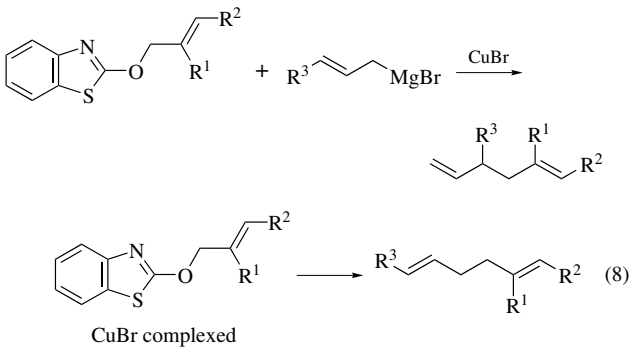
(6)

The control of chemo-, regio-, and stereochemistry in the reactions of allylic electrophiles with two different leaving groups with organocopper reagents is difficult to achieve since many chemo-, regio-, and stereochemical reactions occur together with the desired one.[8] These difficulties can be overcome by using the benzothiazolyl group as one of the leaving groups which is selectively replaced. This has been used for a synthesis of homoallylic pivalates (eq 7).[1]



(7)

2-Allyloxybenzothiazoles. Coupling of these reagents with allylic Grignard reagents in the presence of CuBr allows regioselective synthesis of 1,5-dienes, thus overcoming the difficulties found for different allylic electrophiles.[9] The C–C coupling occurs exclusively in a head-to-tail fashion. Contrary to this the same electrophiles, when complexed with CuBr before the addition of the allylic Grignard reagent, give only 1,5-dienes derived from head-to-head coupling process (eq 8).[10]



(8)

1. Caló, V.; De Nitti, C.; Lopez, L.; Scilimati, A., *Tetrahedron* **1992**, *48*, 6051.
2. Caló, V.; Lopez, L.; Pesce, G.; Calianno, A., *J. Org. Chem.* **1982**, *47*, 4482.
3. Caló, V.; Lopez, L.; Carlucci, W., *J. Chem. Soc., Perkin Trans. 1* **1983**, 2953.
4. Caló, V.; Lopez, L.; Fiandanese, V., *Gazz. Chim. Ital.* **1990**, *120*, 577.
5. Underiner, T. L.; Goering, H. L., *J. Org. Chem.* **1991**, *56*, 2563.
6. (a) Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A. M., *J. Org. Chem.* **1990**, *55*, 2294. (b) Valverde, S.; Bernabé, M.; Gómez, A. M.; Puebla, P., *J. Org. Chem.* **1992**, *57*, 4546.
7. Caló, V.; Lopez, L.; Pesce, G., *J. Chem. Soc., Chem. Commun.* **1986**, 1252.
8. Bäckvall, J. E.; Sellén, M.; Grant, B., *J. Am. Chem. Soc.* **1990**, *112*, 6651.
9. (a) Trost, B. M., *Acc. Chem. Res.* **1980**, *13*, 385. (b) Godschalx, J.; Stille, J. F., *Tetrahedron Lett.* **1980**, *21*, 2595. (c) Julia, M.; Verpeaux, J. N., *Tetrahedron* **1983**, *39*, 3289.
10. Caló, V.; Lopez, L.; Pesce, G., *J. Chem. Soc., Perkin Trans. 1* **1988**, 1301.

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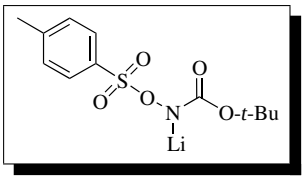
tert-Butyl *N*-Lithio-*N*-(*p*-toluenesulfonyloxy)carbamate



[134953-60-9] $C_{12}H_{16}LiNO_5S$ (MW 293.26)

InChI = 1/C12H17NO5S.Li/c1-9-5-7-10(8-6-9)19(15,16)18-13-11(14)17-12(2,3)4;/h5-8H,1-4H3,(H,13,14);/q;+1/p-1/fC12H16NO5S.Li/q-1;m/rC12H16LiNO5S/c1-9-5-7-10(8-6-9)20(16,17)19-14(13)11(15)18-12(2,3)4/h5-8H,1-4H3

InChIKey = IWLXCCOJEFFKJV-PFCZUCHPCH

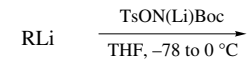
(electrophilic aminating agent for several carbanions;[1] can react with organoboranes to produce *N*-Boc protected primary amines[2])

Solubility: sol THF and diethyl ether.

Preparative Method: prepared from *t*-butyl *N*-(*p*-toluenesulfonyloxy)carbamate and butyllithium at −78 °C in anhydrous THF.

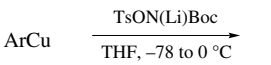
Handling, Storage, and Precautions: should be used immediately as prepared for best results.

Electrophilic Amination. *t*-Butyl *N*-lithio-*N*-(*p*-toluenesulfonyloxy)carbamate (**1**) is prepared from *t*-butyl *N*-(*p*-toluenesulfonyloxy)carbamate, which is easily obtained on a large scale by tosylation of the commercially available *t*-butyl *N*-hydroxycarbamate.[3] (**1**) is an electrophilic aminating reagent and a synthetic equivalent of '$^{+}$NHBoc'. It reacts with alkyllithium reagents (eq 1)[1a] or arylcopper reagents (eq 2)[1b] to provide primary amines in their *N*-Boc protected form.



(1)

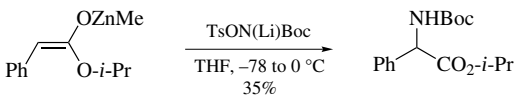
R = Me, 60%; Bu, 71%; *s*-Bu, 42%



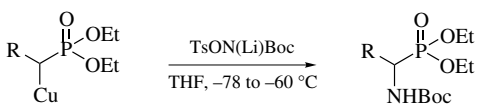
(2)

Ar = Ph, 51%; 2-anisyl, 73%; 2-pyridyl, 53%; 2-thienyl , 47%; 3-furyl, 48%

Zinc ester enolates react with (**1**) to give the corresponding *N*-Boc α-amino carboxylic esters in moderate yield (eq 3).[1a] In contrast, diethyl α-cuprophosphonates give *N*-Boc α-amino phosphonic esters in acceptable yields (eq 4).[1a]



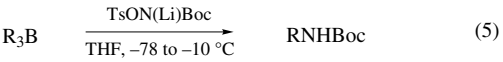
(3)



(4)

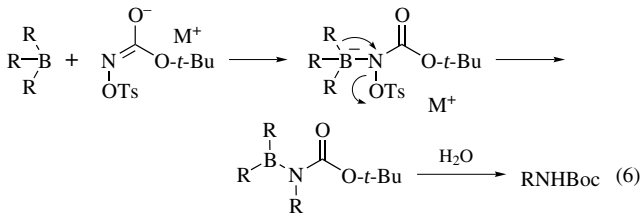
R = Me, 80%; Ph, 50%

Reaction with Organoboranes.[2] Primary and secondary alkylboranes react rapidly at low temperature with (**1**) to give the corresponding *N*-Boc protected primary amines (eq 5). The reaction presumably proceeds via the anionotropic rearrangement of an organoborate complex (eq 6). *N*-Boc protected aniline is obtained from triphenylborane under the same conditions with a yield of 16%. This yield can be increased by using the potassium form of the aminating reagent, which is more reactive with organoboranes.



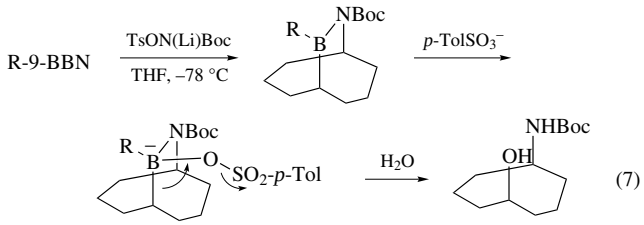
(5)

R = Bu, 81%; *s*-Bu, 30%



(6)

The reaction of alkyl derivatives of 9-borabicyclo [3.3.1]nonane dimer (9-BBN) with (**1**) results in migration of the *B*-cyclooctyl group, producing *N*-Boc-5-aminocyclooctanol (eq 7).



(7)

1. (a) Genêt, J.-P.; Mallart, S.; Greck, C.; Piveteau, E., *Tetrahedron Lett.* **1991**, *32*, 2359. (b) Greck, C.; Bischoff, L.; Hajicek, J.; Genêt, J.-P., *Bull. Soc. Chem. Fr., Part 2* **1994**, *131*, 429.
2. Genêt, J.-P.; Hajicek, J.; Bischoff, L.; Greck, C., *Tetrahedron Lett.* **1992**, *33*, 2677.
3. Carpino, L. A.; Giza, C. A.; Carpino, B. A., *J. Am. Chem. Soc.* **1959**, *81*, 955.

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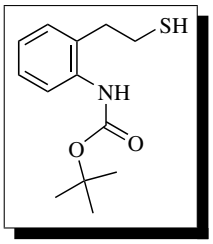
2-[*N*-(*tert*-Butyloxycarbonyl)-aminophenyl]ethanethiol



[193806-48-3] $C_{13}H_{19}NO_2S$ (MW 253.36)

InChI = 1/C13H19NO2S/c1-13(2,3)16-12(15)14-11-7-5-4-6-10(11)8-9-17/h4-7,17H,8-9H2,1-3H3,(H,14,15)/f/h14H

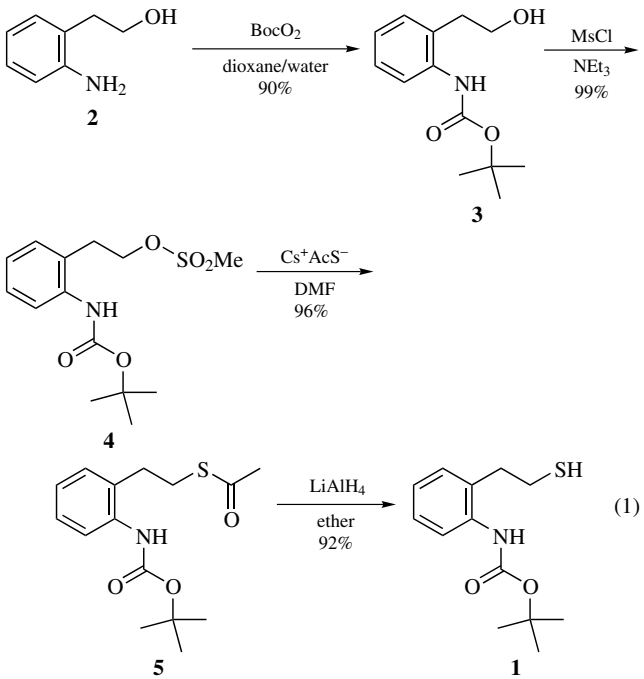
InChIKey = BXPVJMLTVONZLD-YHMJCDSICQ

(reagent used for the generation of acyl radicals under stannane-free conditions)

Physical Data: white solid, mp 44–45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.46 (t, J = 8.1 Hz, 1H), 1.52 (s, 9H), 2.77–2.83 (m, 2H), 2.91 (t, J = 6.9 Hz, 2H), 6.56 (s, 1H), 7.08 (t, J = 7.1 Hz, 1H), 7.15 (dd, J = 7.6, 1.1 Hz, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H).[1]

Solubility: soluble in most organic solvents.

Preparative Methods: the synthesis of **1** was achieved by protection of the amino alcohol **2** with Boc_2O to give the carbamate **3**. Conversion to the mesylate **4** was followed by reaction with cesium thioacetate to give the thiol acetate **5**. Finally, a selective reduction of the thioacetate group afforded **1** (eq 1).[1]

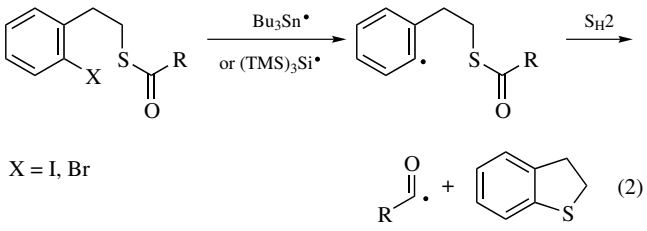


(1)

Introduction. With the initial purpose of generating acyl radicals under oxidative conditions and avoiding the well-known problems of separation, toxicity, and disposal that plague[2] many tin

reagents used in free-radical reactions, **1** was synthesized by Crich and Hao.[1] Although this compound is not a direct free radical precursor itself, the thiol group is easily transformed into a wide variety of thiol esters which, following removal of the Boc group and subsequent conversion of the amine to the corresponding diazonium ion, serve as acyl radical precursors under nonreducing, stannane-free conditions.

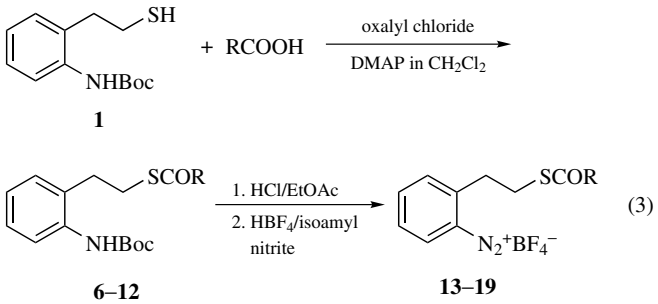
Generation of Acyl Radicals. The generation of acyl radicals from simple thiol esters, either by photochemical methods or in conjunction with silanes and stannanes, is complicated by low quantum yields and lack of reactivity.[3] This problem was circumvented by the inclusion of an additional propagation step, an intramolecular homolytic substitution (S_H2) of an aryl radical on the sulfur atom of a thiol ester carbonyl group (eq 2),[4] in a radical chain sequence.



(2)

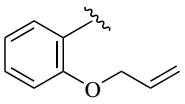
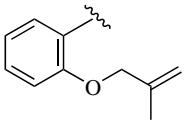
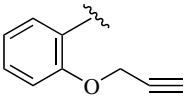
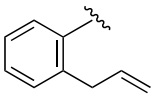
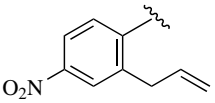
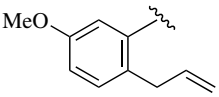
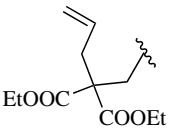
In the initial demonstration of this concept, the aryl radical was obtained by the classic tin method (eq 2). Subsequently, by changing the radical precursor from a halogen to a diazonium ion and working in the presence of an appropriate source of electrons, it was possible to carry out the homolytic displacement reaction under stannane-free, nonreductive conditions.[1] The method is based on work from the Beckwith laboratory,[5] in which it was demonstrated that arenediazonium salts in the presence of electron donors, such as iodide and thiolate ions, can generate aryl radicals in a facile, clean reaction.

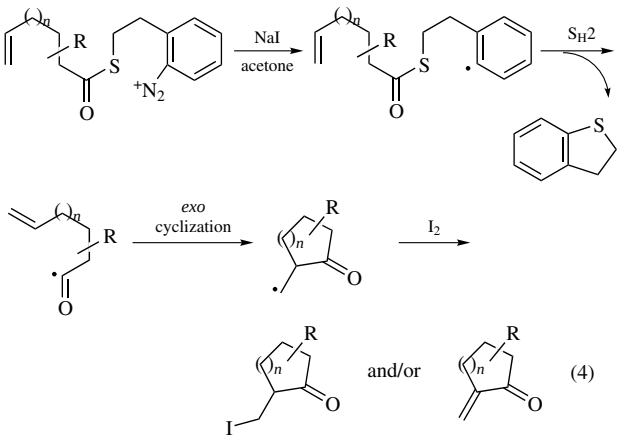
The application of **1** begins with its conversion to the corresponding thiol esters **6–12** from the carboxylic acids. Boc removal with hydrogen chloride in ethyl acetate affords the corresponding hydrochloride salts which are treated with tetrafluoroboric acid and isoamyl nitrite to give the desired diazonium ions **13–19** (eq 3, Table 1).[1] These radical precursors react with NaI in redistilled and degassed acetone at room temperature to afford acyl radicals (eq 4), which undergo cyclization in the *exo* fashion to give various cyclic products **20–28** (Table 2).[1]



(3)

Table 1 Formation of acyl radical precursors from **1**

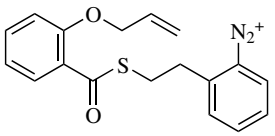
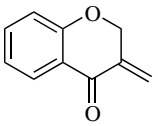
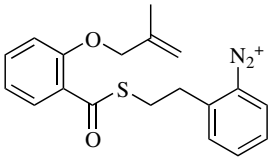
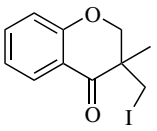
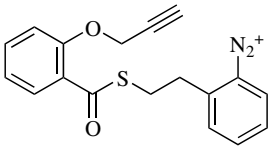
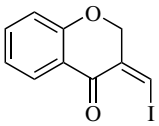
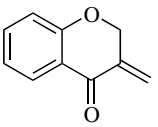
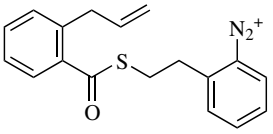
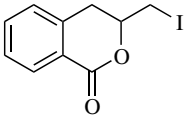
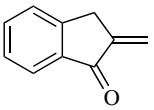
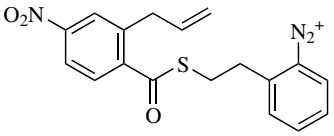
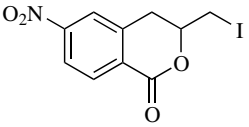
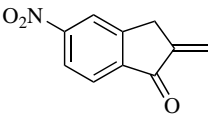
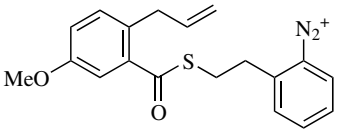
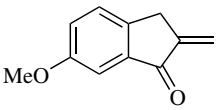
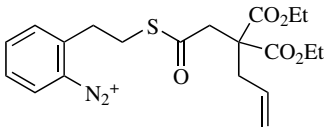
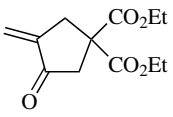
Entry	R	Thiol ester (Yield%)	Radical precursor (Yield%)
1		**6** (82)	**13** (85)
2		**7** (80)	**14** (86)
3		**8** (85)	**15** (85)
4		**9** (80)	**16** (81)
5		**10** (80)	**17** (84)
6		**11** (77)	**18** (86)
7		**12** (81)	**19** (84)

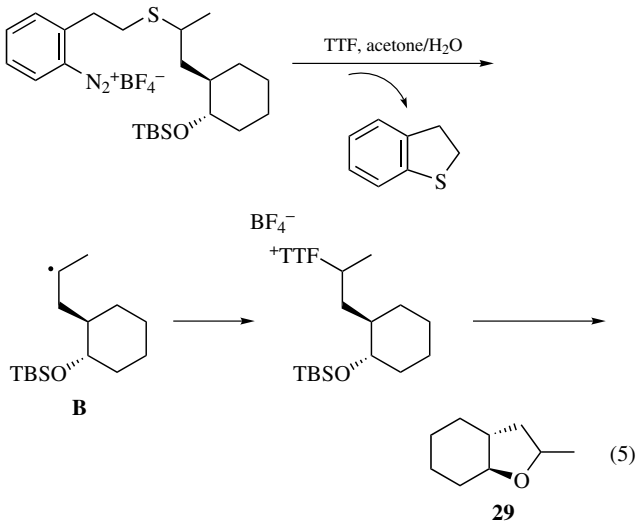


(4)

Generation of Alkyl Radicals. Murphy[6] has utilized a closely related synthetic scenario for the nonreducing generation of alkyl radicals and, thereby, heterocyclic compounds as, for example, **29** (eq 5). In this sequence homolytic substitution at sulfur of a thioether **30** afforded an alkyl radical; tetrathiafulvalene (TTF) served both as a source of electrons and, via its radical cation, as the initial radical trap (eq 5).

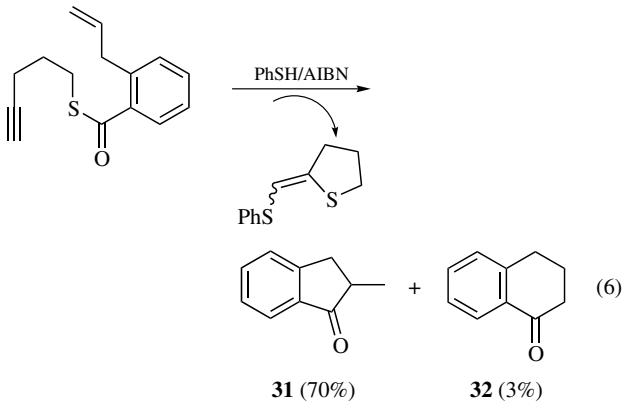
Table 2 Generation and cyclization of acyl radicals

Radical precursor	Product 1 (Yield%)	Product 2 (Yield%)
 **13**		 **20** (81)
 **14**	 **21** (85)	
 **15**	 **22** (50)	 **20** (25)
 **16**	 **23** (10)	 **24** (75)
 **17**	 **25** (37)	 **26** (trace)
 **18**		 **27** (88)
 **19**		 **28** (70)



(5)

Benati[7] has extended the general concept of S_H2 at sulfur with the introduction of *S*-(4-pentynyl)thiol esters, which are activated with thiophenol and a radical initiator (eq 6) .



(6)

Related Reagents. 2-(2-Iodophenyl)ethanethiol; 2-(2-Iodophenyl)-2-methylpropanethiol; 2-(2-Bromophenyl)-2-methylpropanethiol; 2′-Iodobiphenyl-2-thiol; Dimethylaluminum Complex.

1. Crich, D.; Hao, X., *J. Org. Chem.* **1997**, *62*, 5982.
2. Studer, A.; Amrein, S., *Synthesis* **2002**, 835.
3. Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I., *Chem. Rev.* **1999**, *99*, 1991.
4. Crich, D.; Yao, Q., *J. Org. Chem.* **1996**, *61*, 3566.
5. (a) Meijs, G. F.; Beckwith, A. L. J., *J. Am. Chem. Soc.* **1986**, *108*, 5890. (b) Beckwith, A. L. J.; Meijs, G. F., *J. Org. Chem.* **1987**, *52*, 1922. (c) Abeywickrema, A. N.; Beckwith, A. L. J., *J. Am. Chem. Soc.* **1986**, *108*, 8227.
6. (a) Bashir, N.; Murphy, J. A., *Chem. Commun.* **2000**, 627. (b) Callagan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A., *J. Chem. Soc., Perkin Trans 1* **1999**, 995.
7. Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S., *Org. Lett.* **2003**, *5*, 1313.

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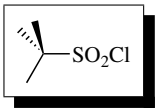
tert-Butylsulfonyl Chloride



[10490-22-9] $C_4H_9ClO_2S$ (MW 156.63)
InChI = 1/C4H9ClO2S/c1-4(2,3)8(5,6)7/h1-3H3
InChIKey = WFBUQJSXXDVYFZ-UHFFFAOYAI

(sulfonylating agent, percursor to *tert*-butyl cations)

Alternate Name: 2-methylpropane-2-sulfonyl chloride, trimethylmethanesulfonyl chloride, 2-methyl-2-propanesulfonyl chloride, BusCl.

Physical Data: white solid, mp 95 °C.

Solubility: soluble in most common organic solvents.

Form Supplied in: not commercially available.

Preparative Methods: from *tert*-butylmagnesium chloride and excess sulfur dioxide or from the sulfinic acid.[1]

Purity: vacuum sublimation.[1]

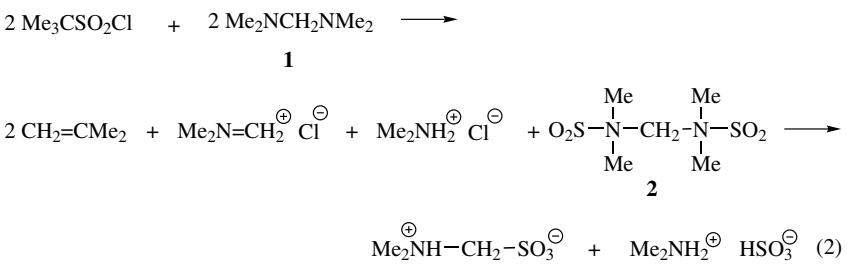
Handling, Storage, and Precaution: this reagent is not stable at ambient temperature, decomposing with a half-life of approx. 34 h at 35 °C to *t*-butyl chloride, isobutylene, sulfur dioxide, and hydrogen chloride.[1]

Source of *tert*-Butyl Cation: *tert*-Butylation of Aromatics. Physical organic studies have demonstrated that *tert*-butylsulfonyl chloride decomposes cleanly to the *tert*-butyl cation in water over a pH range 3.5 to 13.0. Clean *tert*-butyl cation formation is also the only significant reaction in methanol-chloroform. The subsequent product spectrum is a function of the reaction conditions.[2] *tert*-Butylsulfonyl chloride, is used for the *tert*-butylation of aromatic compounds in a Friedel-Crafts desulfonylative alkylation[3]in the presence of aluminum chloride-nitromethane as catalyst at 25 °C (eq 1). Alkylation products were obtained free of contamination by the sulfonylation product.

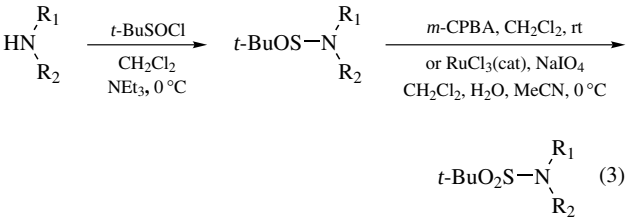
$$\text{Ar-H} + (CH_3)_3CSO_2Cl \xrightarrow{AlCl_3} \text{Ar-C}(CH_3)_3 + SO_2 + HCl \quad (1)$$

Aminal Cleavage. In contrast to aromatic sulfonyl chlorides, which effect cleavage of aminals exclusively with formation of iminium salts and sulfonamides, *tert*-butylsulfonyl chloride functions exclusively as a hydrogen chloride and sulfur dioxide donator to aminal **1** (eq 2).[4] In addition to iminium and ammonium salts the formation of an aminal-sulfur dioxide adduct **2** takes place. This latter can be hydrolyzed to dimethylaminomethanesulfonic acid and dimethylammonium hydrogensulfite.

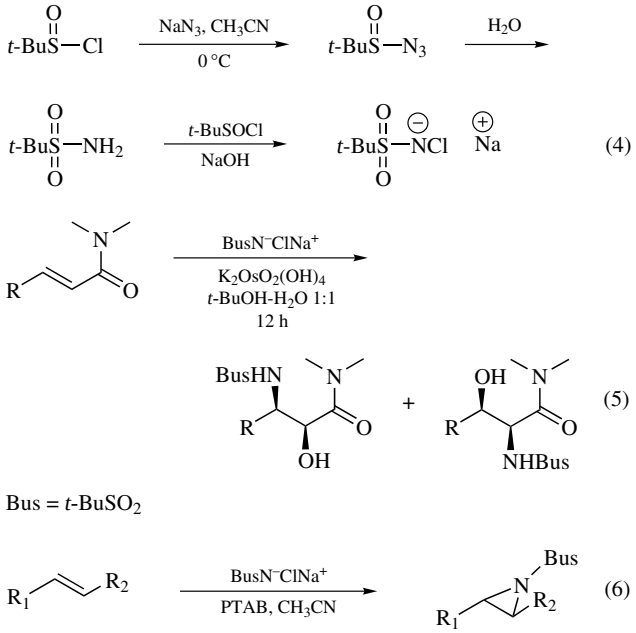
***tert*-Butylsulfonyl (Bus), as a Protecting Group for Amines.** Because of their stability to a wide variety of reaction conditions, sulfonamides are robust amine protecting groups. The high stability can nevertheless be problematic as it often requires harsh conditions for deprotection. The *tert*-butylsulfonamides were introduced by Sun and Weinreb as amine protecting groups capable of withstanding metallation conditions yet removable under



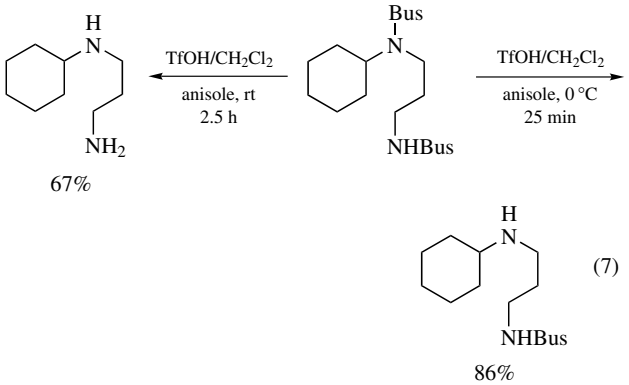
mild acidic conditions.[5] The relative lack of reactivity of *tert*-butylsulfonyl chloride toward amines, resulted in the development of a two step introduction protocol employing the much more reactive *tert*-butylsulfinyl chloride followed by oxidation of the sulfonamide with either *m*-CPBA or sodium *meta*-periodate in the presence of catalytic ruthenium trichloride (eq 3).[5]



It was subsequently found by Sharpless and co-workers that the chloramine derived (eq 4) from *tert*-butylsulfonamide is an effective reagent for the osmium-catalyzed aminohydroxylation of α,β-unsaturated amides (eq 5). In conjunction with a phase transfer catalyst, this chloramine also enables aziridination of alkenes (eq 6).[6]



Bis-protected amines generated by the above methods were found to be resistant to 0.1 N HCl in methanol, to 0.1 N TFA in methanol, both at room temperature for 1 h, and to pyrolysis at 180 °C. However, the sulfonamide was cleaved by 0.1 N trifluoromethanesulfonic acid in dichloromethane in the presence of anisole. Noteworthy is the more rapid removal of the group from secondary amines which enables their selective deprotection in the presence of Bus-protected primary amines (eq 7).[5]



BusNEt$_2$ as a Polar Aprotic Solvent. The relative stability of sulfonamides toward nucleophilic and basic reagents also raises the possibility of their application as polar aprotic solvents, as investigated by Richey and Farkas.[7] *N,N*-Diethyl *tert*-butylsulfonamide has low solubility in water (7 mg/mL) but is miscible with toluene. Organometallic lifetimes in BusNEt$_2$ range from <5 min (BuLi) to 14 h (MeLi). The potential of BusNEt$_2$ as a polar aprotic solvent may be estimated from the its Taft π^* and β-parameters (0.65 and 0.59, respectively) which, while short of dimethyl sulfoxide (1.00 and 0.76) and dimethylformamide (0.88 and 0.69), give an indication of the possibilities.[7]

Related Reagents. *tert*-Butylsulfinyl Chloride; Di-*tert*-butyl Disulfide; Benzenesulfonyl Chloride; Methanesulfonyl Chloride; 2-Nitrobenzenesulfonyl Chloride;[8] 4-Nitrobenzenesulfonyl Chloride;[8] 2,4-Dinitrobenzenesulfonyl Chloride.[9]

1. van Aller, R. T.; Scott, R. B.; Brockelbank, E. L., *J. Org. Chem.* **1966**, *31*, 2357.
2. King, J. F.; Lam, J. Y. L.; Dave, V., *J. Org. Chem.* **1995**, *60*, 2831.
3. Olah, G. A.; Nishimura, J.; Yamada, Y., *J. Org. Chem.* **1974**, *39*, 2430.
4. Boehme, H.; Pindur, G., *Chem. Ber.* **1978**, *111*, 3294.
5. Sun, P.; Weinreb., *J. Org. Chem.* **1997**, *62*, 8604.
6. Gontcharov, A. V.; Liu, H.; Sharpless, K. B., *Org. Lett.* **1999**, *1*, 783.
7. Richey, H. G.; Farkas, J., *J. Org. Chem.* **1987**, *52*, 479.
8. Fukuyama, T.; Jow, C.-K.; Cheung, M., *Tetrahedron Lett.* **1995**, *36*, 6373.
9. Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T., *Tetrahedron Lett.* **1997**, *38*, 5831.

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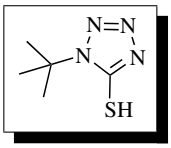
tert-Butyltetrazolylthiol



[7624-35-3] $C_5H_{10}N_4S$ (MW 158.23)

InChI = 1/C5H10N4S/c1-5(2,3)9-4(10)6-7-8-9/h1-3H3,(H,6,8,10)/f/h10H

InChIKey = TYVQFMFAGGWJLV-KZFATGLACI

(used in the preparation of stable *cis*-selective Julia-Kocienski olefination reagents)

Alternate Name: 1-*tert*-butyl-1*H*-tetrazolyl-5-thiol.

Physical Data: mp 97–98 °C.

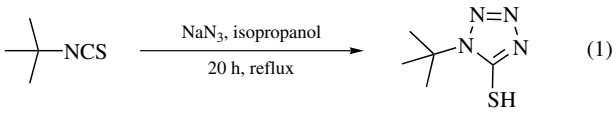
Solubility: soluble in EtOH.

Preparative Methods: readily synthesized from commercially available materials.

Purification: recrystallized from cyclohexane.

Handling, Storage, and Precautions: normal laboratory practices.

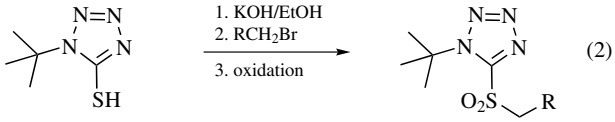
This reagent is prepared in good yield from the reaction of *tert*-butyl isothiocyanate (readily available commercially) with sodium azide (eq 1).[1,2]



(1)

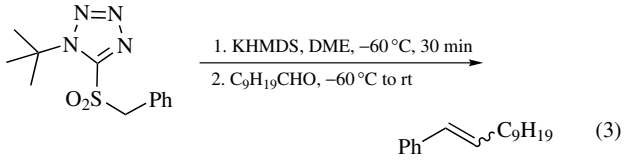
73% yield

Alkylation of this thiol with 1-bromopentane, benzyl bromide, and allyl bromide proceeds in excellent yield; subsequent oxidation to the sulfones is rather substrate dependent and the yields are variable (eq 2).



(2)

The sulfones prepared can be metallated with KHMDS at low temperature and, unlike the related benzothiazolyl and 1-phenyl-1*H*-tetrazolyl systems, show excellent stability with little tendency to self-condense. Selectivities observed in olefinations are good to excellent in favor of the *Z*-isomers (eq 3).



(3)

95% yield

<1:99 *E*:*Z*

Stabilization of the intermediate anion through conjugation tends to lead to higher *Z*-selectivity, which is complementary to the behavior of the related *E*-selective 1-phenyl-1*H*-tetrazolyl sulphones.[1]

Other work has been carried out on the alkylation of 1-*tert*-butyl-1*H*-tetrazolyl-5-thiol with diazoalkyl reagents and the subsequent photochemical behavior of the adducts.[2,3]

Related Reagents. Benzothiazole-2-thiol; 1-Phenyl-1*H*-tetrazolyl-5-thiol; Pyridine-2-thiol.

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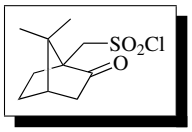
1. Kocienski, P. J.; Bell, A.; Blakemore, P. R., *Synlett* **2000**, 365.
2. Quast, H.; Bieber, L., *Chem. Ber.* **1981**, *114*, 3253.
3. Quast, H.; Nahr, U., *Chem. Ber.* **1983**, *116*, 3427.

Andrew Lund
Peakdale Molecular Ltd, Chapel-en-le-Frith, UK

C

10-Camphorsulfonyl Chloride[1]



(1*R*)
[21286-54-4] $C_{10}H_{15}ClO_3S$ (MW 250.75)
InChI = 1/C10H15ClO3S/c1-9(2)7-3-4-10(9,8(12)5-7)6-15(11,13)14/h7H,3-6H2,1-2H3/t7-,10-/m0/s1
InChIKey = BGABKEVTHIJBIW-XVKPBYJWBY
(1*S*)
[39262-22-1]
InChI = 1/C10H15ClO3S/c1-9(2)7-3-4-10(9,8(12)5-7)6-15(11,13)14/h7H,3-6H2,1-2H3/t7-,10-/m1/s1
InChIKey = BGABKEVTHIJBIW-GMSGAONNBT
(±)
[6994-93-0]
InChI = 1/C10H15ClO3S/c1-9(2)7-3-4-10(9,8(12)5-7)6-15(11,13)14/h7H,3-6H2,1-2H3
InChIKey = BGABKEVTHIJBIW-UHFFFAOYAQ

(enantiomeric excess determination;[2] chemical resolution;[3] synthesis of chiral auxiliaries;[4] chiral precursor for natural product synthesis;[1] synthesis of chiral reagents[5])

Physical Data: mp 65–67 °C; (1*S*)-(+): $[\alpha]_D + 32.1°$ (*c* 1, $CHCl_3$).

Solubility: sol CH_2Cl_2; slightly sol ether; insol H_2O.

Form Supplied in: both enantiomers and the racemic sulfonyl chloride are commercially available.

Preparative Methods: can be prepared from 10-camphorsulfonic acid upon treatment with phosphorus(V) chloride or thionyl chloride.[6]

Purification: crystallized from hexane or from MeOH.

Handling, Storage, and Precautions: corrosive and moisture-sensitive. This reagent should be handled in a fume hood.

Original Commentary

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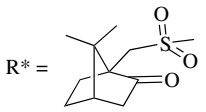
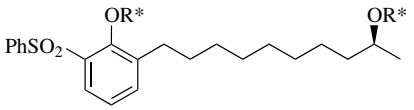
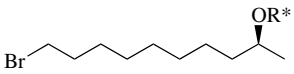
Université de Montréal, Québec, Canada

Reagent for Determination of Enantiomeric Excesses and for Chemical Resolution of Alcohols and Amines. 10-Camphorsulfonyl chloride has been widely used as a chiral derivatizing agent for the assay of enantiomeric purity of alcohols and amines by NMR techniques.[2] A typical procedure for the preparation of the sulfonate ester or sulfonamide involves mixing a solution of the alcohol or amine in CH_2Cl_2 with camphorsulfonyl chloride in the presence of an amine base (Et_3N, py, or DMAP). This reagent has been particularly valuable for determining the enantiomeric purity of secondary alcohols (**1**, **2**) and β-hydroxy esters (**3**).[7]

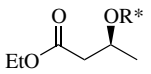




(**1**)

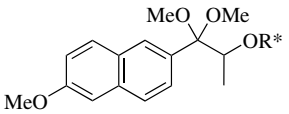


(**2**)



(**3**)

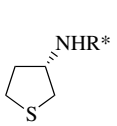
In some cases (**3**), the addition of a chiral shift reagent ($Eu(hfc)_3$) is necessary to obtain baseline separation of the signals corresponding to the β-proton of both diastereomers by ^1H NMR. Diastereomeric mixtures derived from secondary alcohols have also been analyzed by HPLC.[8] The resolution of a secondary alcohol (**4**) could be achieved by a selective crystallization of one of the two diastereomeric camphorsulfonate esters.[3]



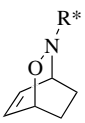
(**4**)

The enantiomeric purities of primary and secondary amines have also been established by ^1H NMR spectroscopy by their conversion into the corresponding sulfonamide. These derivatives often produce crystalline compounds that are suitable for X-ray crystallographic studies. For example, the enantiomeric purities of amines (**5**),[9] (**6**),[10] and (**7**)[11] were determined by ^1H NMR spectroscopy and the absolute stereochemistry of (**7**) was unequivocally established by X-ray crystallography.

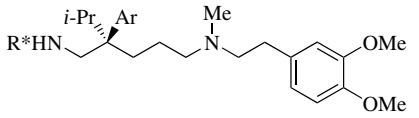
A general protocol for the HPLC separation of diastereomeric camphorsulfonamides[12] derived from racemic α-amino acids has been developed (eq 1).[13] More complex amino acids, such as (**8**), were successfully analyzed by this procedure.[14]



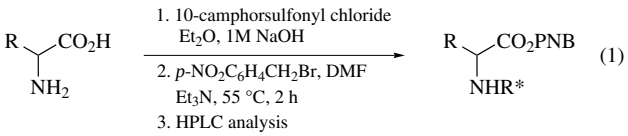
(**5**)



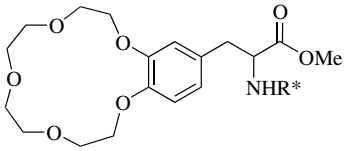
(**7**)



(**6**) Ar = 3,4-$(OMe)_2C_6H_3$

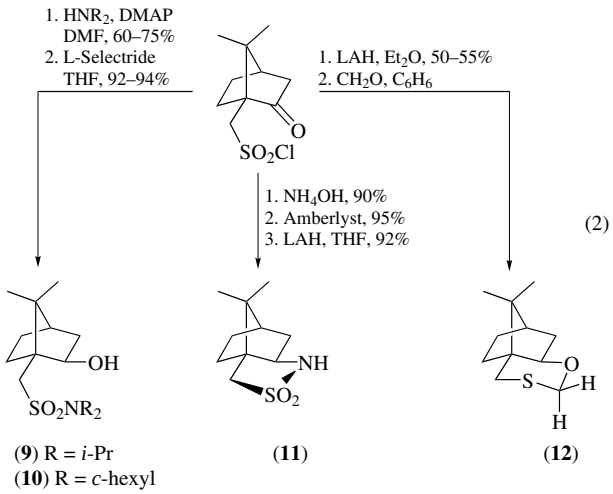


(1)



(**8**)

Synthesis of Chiral Auxiliaries. Their availability and crystalline nature has made camphor derivatives the precursors of choice for the design and synthesis of chiral auxiliaries.[4] 10-Camphorsulfonyl chloride is the starting material for the synthesis of chiral auxiliaries (**9**)–(**12**) (eq 2). Sulfonamides (**9**) and (**10**)[15] have been used as chiral auxiliaries in a number of reactions, e.g. the Lewis acid-catalyzed Diels–Alder reaction, the [3 + 2] cycloaddition of a nitrile oxide to an acrylate, and the stereoselective conjugate addition reaction of organocopper reagents to α,β-unsaturated esters.[4]



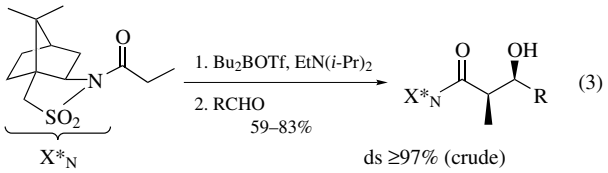
(2)

(**9**) R = *i*-Pr
(**10**) R = *c*-hexyl

(**11**)

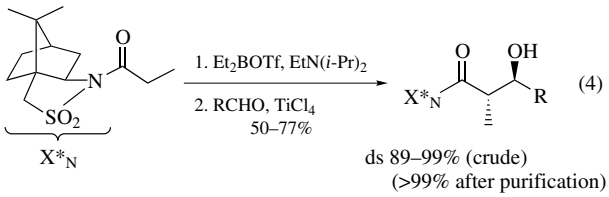
(**12**)

In addition to being an efficient chiral controller in a number of stereoselective transformations of chiral acrylates, (i.e. the Diels–Alder reaction,[4] the conjugate reduction,[16] the asymmetric dihydroxylation,[17] and the nitrile oxide cycloaddition[18]) the bornanesultam (**11**)[19] has been shown to be an exceptionally efficient chiral auxiliary for stereoselective aldol condensations (eqs 3 and eq 4). Depending upon the reaction conditions, *N*-propionylsultam can produce either the *syn* or *anti* aldol product with an excellent diastereoselectivity.[20] Furthermore, good diastereoselectivities are also observed for the corresponding acetate aldol reaction (eq 5).[21]



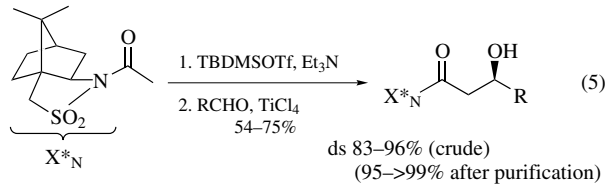
(3)

ds ≥97% (crude)
(>99% after purification)



(4)

ds 89–99% (crude)
(>99% after purification)



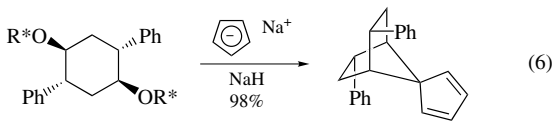
(5)

ds 83–96% (crude)
(95–>99% after purification)

Oxathiane (**12**) has been shown to be an efficient chiral auxiliary in the nucleophilic addition to carbonyl compounds.[22]

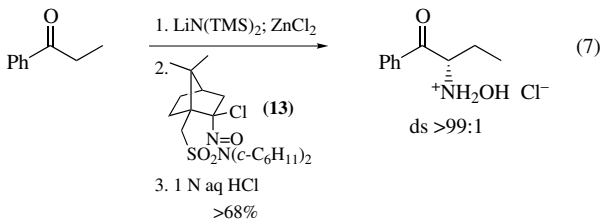
10-Camphorsulfonyl chloride has also been widely used as a useful precursor to chiral dienophiles in hetero-Diels–Alder reactions.[23]

An elegant use of the chirality and the leaving group ability of the camphorsulfonate ester has been reported in the synthesis of a chiral C_2 symmetric cyclopentadienyl ligand (eq 6).[24]



(6)

Synthesis of Chiral Reagents. An efficient chiral α-chloro-α-nitroso reagent derived from 10-camphorsulfonyl chloride (1. Cy_2NH; 2. NH_2OH; 3. *t*-BuOCl; 70–78%) has been developed for the asymmetric α-amination of ketone enolates (eq 7).[25] The resulting β-keto *N*-hydroxylamine can be converted to the *anti*-1,2-hydroxyamine under reducing conditions ($NaBH_4$; Zn, HCl, AcOH).

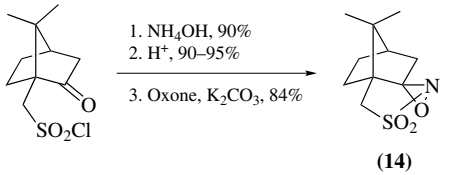


(7)

ds >99:1

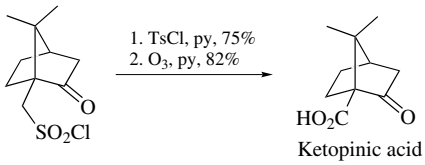
Several oxaziridines related to (**14**)[5] (eq 8) have been used, most notably in the enantioselective oxidation of sulfides to sulfoxides,[26] of selenides to selenoxides,[27] and of alkenes to oxiranes.[28] It is also the reagent of choice for the hydroxylation of lithium and Grignard reagents[29] and for the asymmetric

oxidation of enolates to give α-hydroxy carbonyl compounds.[5,30] A similar chiral fluorinating reagent has also been developed.[31]



(14) (8)

Chiral Precursor for Natural Product Synthesis. 10-Camphorsulfonyl chloride has been used as a chiral starting material for the synthesis of a number of products[1] such as ketopinic acid[32] (eq 9), which has been used to resolve alcohols[33] and hemiacetals.[34]

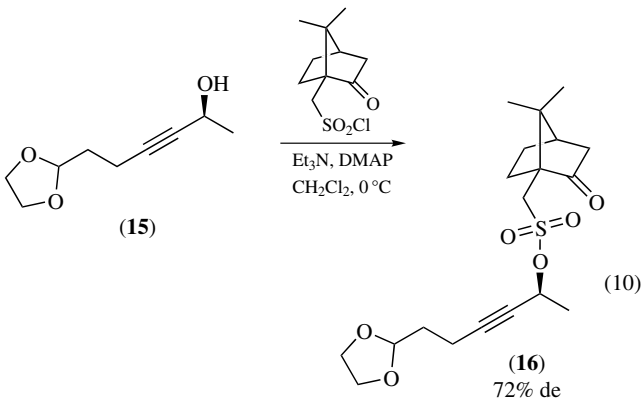


Ketopinic acid (9)

First Update

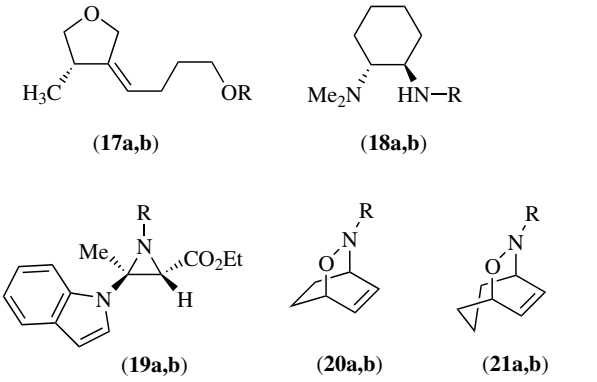
Qingwei Yao
Northern Illinois University, DeKalb, IL, USA

Determination of Enantiomeric Excesses of Chiral Alcohols, Amines, and Related Compounds.[35–39] 10-Camphor sulfonyl chloride continues to be used extensively as a convenient derivatizing agent for chiral alcohols, amines, and related compounds for determination of their enantiomeric access or verification of their optical purity. For example, the secondary propargyl alcohol **15** was converted to the (*S*)-10-camphorsulfonate ester **16** (eq 10) and the de determined by NMR spectroscopy.[35]



(15) (16) 72% de (10)

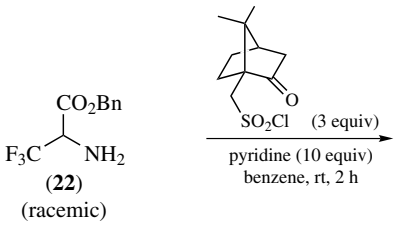
Other examples of compounds whose ee's were determined using (*S*)-(+)-10-camphorsulfonyl chloride as the chiral derivatizing reagent include alcohol **17a**,[36] amine **18a**,[37] aziridine **19a**,[38] and the cyclic hydroxylamines **20a** and **21a**.[39]



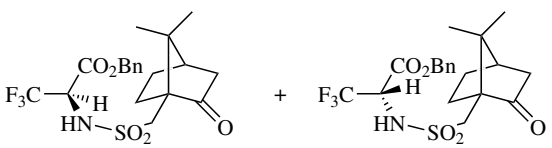
(17a,b) (18a,b) (19a,b) (20a,b) (21a,b)

a: R = H
b: R = (*S*)-camphorsulfonyl

Resolution and Determination of Absolute Configuration of Chiral Amines, Alcohols, and Related Compounds.[40–51] Camphorsulfonyl chloride can be used as a resolving reagent for chiral amines, alcohols, and binaphthols. Derivatives of camphorsulfonates and camphorsulfonamides are generally crystalline compounds and frequently form crystals suitable for X-ray analysis. For example, racemic 3,3,3-trifluoroalanine derivative **22** was resolved into optically pure sulfonamides **23a** and **23b** by derivatization with (1*S*)-camphorsulfonyl chloride followed by HPLC separation (eq 11).[40] Upon recrystallization from ethyl acetate–hexane (1:5), isomer **23a** forms white needles and X-ray analysis established its configuration as (*R*,*S*).



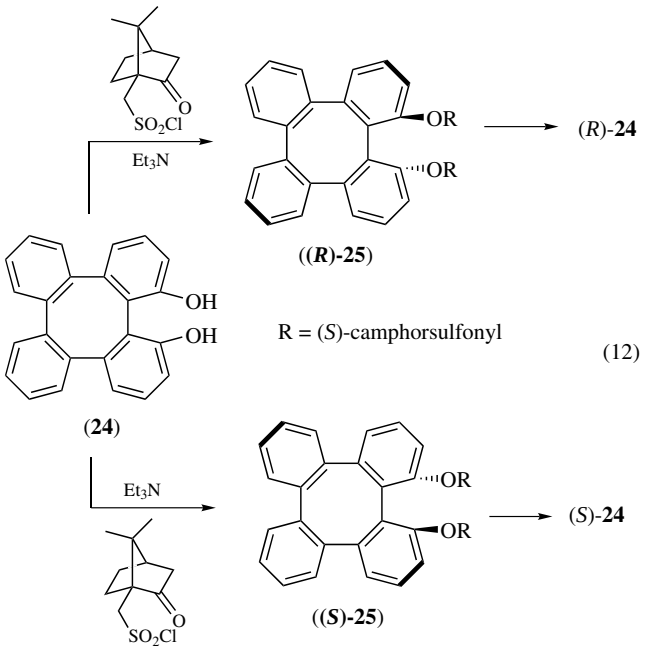
(22) (racemic)



(23a) (*R*,*S*) (white crystal) (23b) (*S*,*S*) (oily) (11)

Camphorsulfonyl chloride has proved to be quite a general resolving agent for analogs of binaphthol as exemplified by the resolution of 1,16-dihydroxytetraphenylene **24** (eq 12).[41]

Other axially chiral molecules that were resolved with camphorsulfonyl chloride include binaphthols **26** and **27**, the dihydroxylbiscarbazoles **28**, biflavone **29**, 2-diarylphosphino-20-methoxy-1,10-binaphthalenes **30**, phenol **31** and alcohol **32** with axial chirality about a C–N bond, and the amino[2.2]paracyclophane **33**.[42–48]



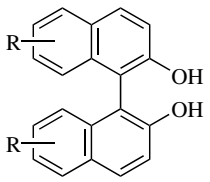
Chemical resolution of racemic 18-methoxycoronaridine (18-MC) **34** was achieved by the formation and chromatographic separation of the diastereomeric sulfonamides **35** (eq 13).[49] The key to the formation of the sulfonamides was the use of potassium bis(trimethylsilyl)amide as the base in this reaction.

The naturally occurring azedaralide **36** was obtained by total synthesis and resolution of its racemate through the formation of enol camphorsulfonate esters. The absolute stereochemistry of the (+)-enantiomer was confirmed by X-ray crystal structure analysis of its (1*S*)-10-camphorsulfonate ester **37**.[50]

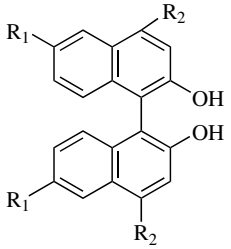
Amides such as the 3,4-dihydropyrimidin-2(1*H*)-one **38** can also be resolved in the form of their camphorsulfonamides (eq 14).[51] Regioselective sulfonylation of the dianion of **38** with (*S*)-camphorsulfonyl chloride furnished a mixture of sulfonamides **39a** and **39b**. The diastereoisomers were then resolved by column chromatography, and the absolute configuration of **39a** was verified by X-ray crystallography of a subsequent derivative.

Synthesis of Chiral Auxiliaries for Diastereoselective Synthesis.[52–56] (1*S*)-(+)-10-Camphorsulfonyl chloride and its enantiomer continue to serve as building blocks for a number of useful chiral auxiliaries.[52–56] For example, in an effort to develop a chiral version of Lossen reaction[55] as a vehicle to desymmetrize *meso*-hydroxamic acids, the camphorsulfornyl group was introduced as both an activator and a chiral director. Methanolysis of camphorsulfonate ester **41** derived from the norbornene-fused *N*-hydroxamic acid **40** led to the formation of the carbamate product in 84% yield and modest ee (33%) (eq 15).[56]

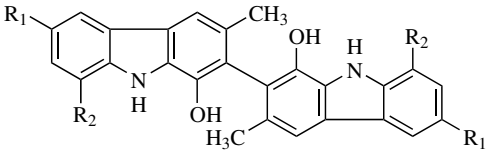
Synthesis of Chiral Ligands for Titanium Alkoxide-promoted Addition of Dialkylzinc to Aldehydes and Ketones. Camphorsulfonyl-derived sulfonamides have been synthesized and screened as ligands for titanium alkoxide-promoted addition of dialkylzinc to aldehydes and ketones. The first example involved the conversion of (*S*)-(+)-camphorsulfonyl chloride to its *N*-benzyl sulfonamide, which was reduced by $NaBH_4$ to afford the diastereomeric hydroxysulfonamides **42** and **43** (eq 16).[57] These ligands were tested in the titanium-catalyzed diethylzinc addition to benzaldehyde.[58–60] Only the exo-epimer **42** turned out to give high levels of stereoselectivity (eq 17).



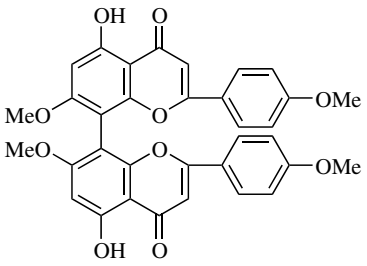
(**26a**), R = H; (**26b**), R = 3-Br
(**26c**), R = 4-Br; (**26d**), R = 6-OMe
(**26e**), R = 7-OMe



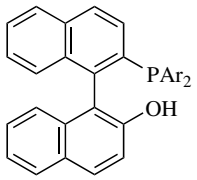
(**27a**), R_1 = H; R_2 = C_4H_9
(**27b**), R_1 = C_4H_9; R_2 = C_4H_9
(**27c**), R_1 = C_8H_{17}; R_2 = C_8H_{17}



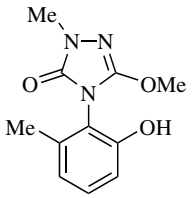
(**28a**), R_1 = R_2 = H
(**28b**), R_1 = OMe; R_2 = H
(**28c**), R_1 = R_2 = OMe



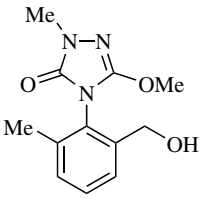
(**29**)



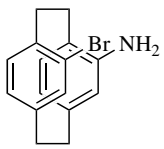
(**30a**), Ar = Ph
(**30b**), Ar = p-C_6H_5



(**31**)

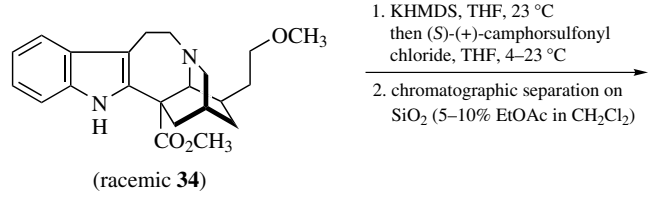


(**32**)

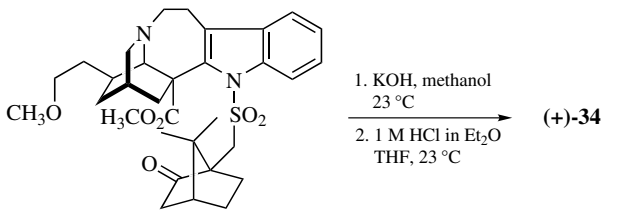


(**33**)

Most of the efforts in this area centered on the synthesis of bis-camphorsulfonamides from either a chiral or an achiral diamine scaffold.[61,62] The optimum derivative was found to be **44**, which proved to be an excellent ligand for the $Ti(O^iPr)_4$-catalyzed addition of Et_2Zn to ketones (eq 18).[63]



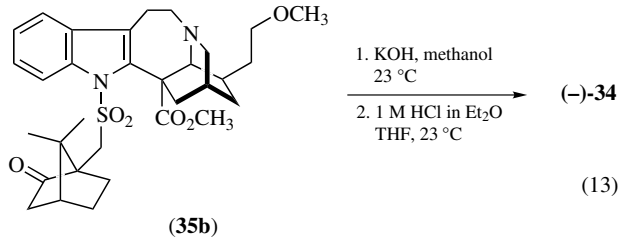
(racemic **34**)



(**35a**)

(+)-34

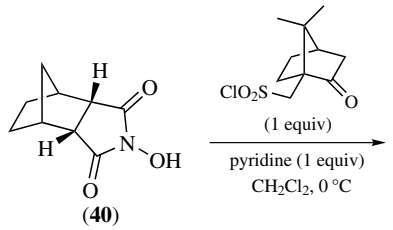
and



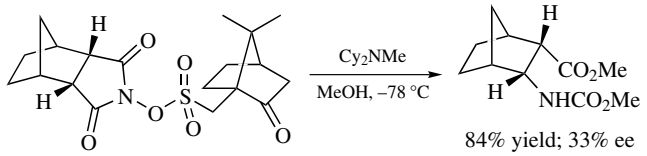
(**35b**)

(–)-34

(13)



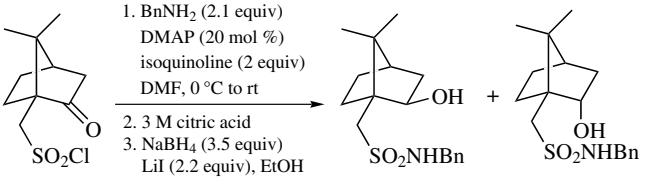
(**40**)



(**41**)

84% yield; 33% ee

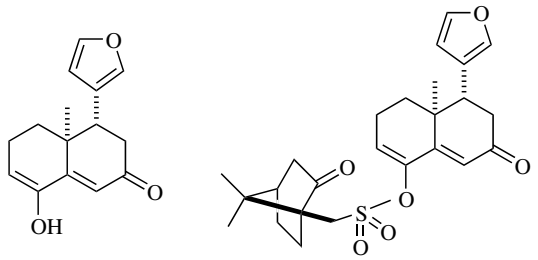
(15)



(**42**), 73%

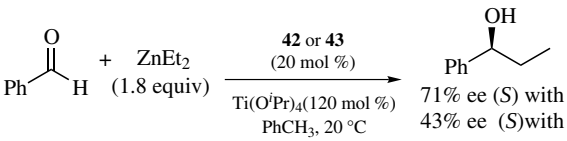
(**43**), 9%

(16)



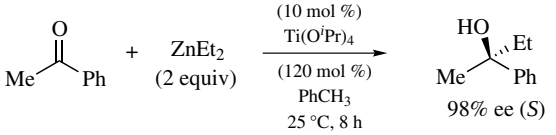
(**36**)
(+)-azedaralide

(**37**)

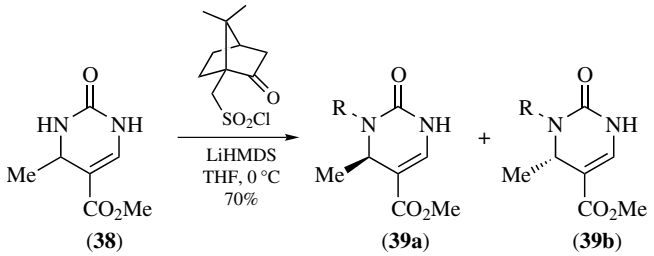


71% ee (*S*) with **42**
43% ee (*S*)with **43**

(17)



98% ee (*S*)



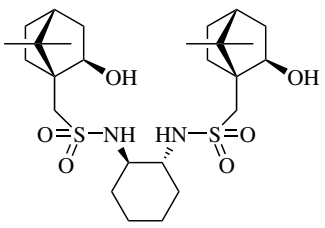
(**38**)

(**39a**)

(**39b**)

R = (*S*)-camphorsulfonyl

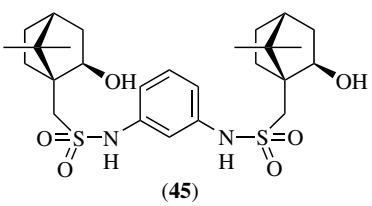
(14)



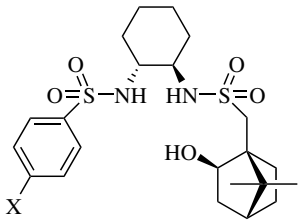
(**44**)

(18)

Similar ligands have been synthesized from aromatic diamines. For example, ligand **45** can be readily assembled from 1,3-benzenediamine, (*S*)-(+)-camphorsulfonyl chloride, and a reducing reagent.[64,65] Good enantioselectivity for the addition of Et_2Zn to benzaldehyde[64] and excellent enantioselectivity for the addition of Me_2Zn to ethyl phenyl ketone[65] were observed with this reagent.

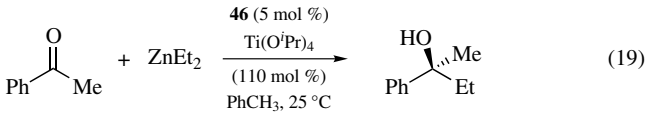


(**45**)

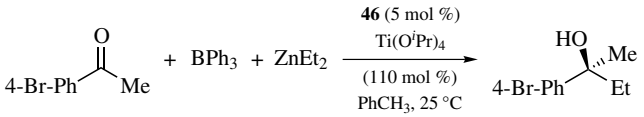


(**46a**), X = Me
(**46b**), X = OMe

Mixed bis-sulfonamide ligands of the type **46** were also prepared and shown to be highly effective for the addition of organozinc reagents to ketones (eqs 19 and 20).[66,67]

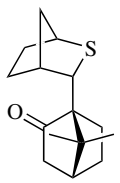


55% yield, >99% ee with **46a**
65% yield, >99% ee with **46b** (19)

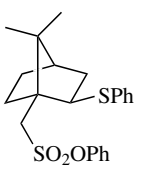


with **46a**, 120 h, 90% yield, >99% ee
with **46b**, 20 h, 96% yield, >99% ee (20)

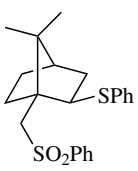
As Precursor for the Synthesis of Chiral Organosulfur and Organoselenium Catalysts or Reagents. The increasing popularity of chiral organosulfur and organoselenium reagents in organic chemistry has prompted a tremendous amount of effort in the synthesis of new organosulfur and organoselenium compounds. The usefulness of 10-camphorsulfonyl chloride as a starting material for the preparation of such molecules is shown by the synthesis of chiral sulfides **47**–**49** and chiral selenides **50**–**52**.[68,69] Compounds **48**–**52** were all prepared from the common intermediate (*S*)-camphorsulfonate **53** derived (*S*)-camphorsulfonyl chloride.[69]



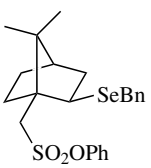
(**47**)



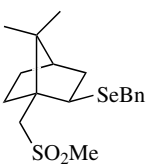
(**48**)



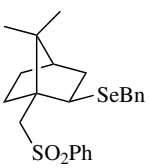
(**49**)



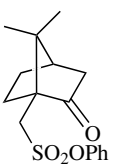
(**50**)



(**51**)

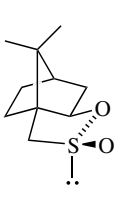


(**52**)

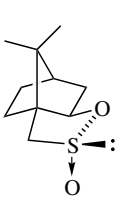


(**53**)

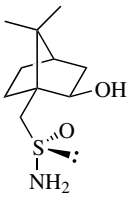
A number of enantiopure sulfinic acid derivatives, including sultines **54** and **55**, sulfinamides **56**–**59**, sulfinimines **60** and **61**, and the chiral sulfoxide **62**, were synthesized from (1*S*)-camphorsulfinic acid that was formed by reduction of (1*S*)-camphorsulfonyl chloride with sodium borohydride.[70]



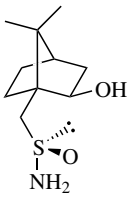
(**54**)



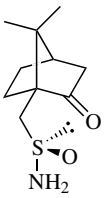
(**55**)



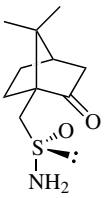
(**56**)



(**57**)

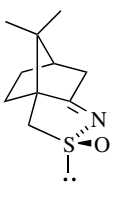


(**58**)

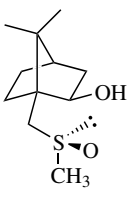


(**59**)

(**60**)

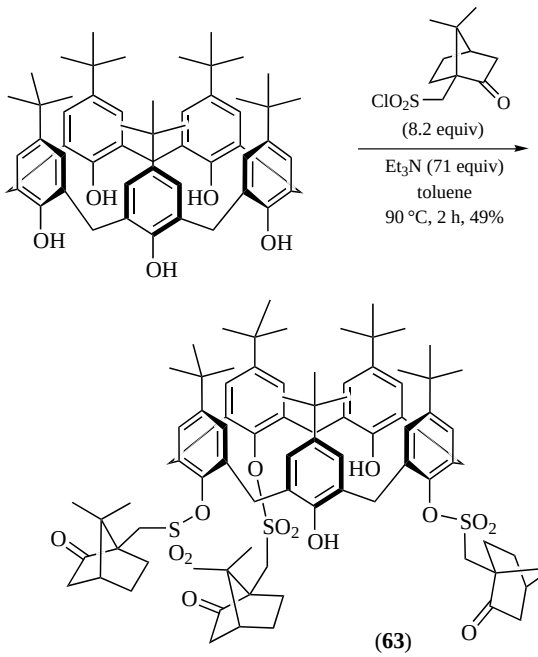


(**61**)

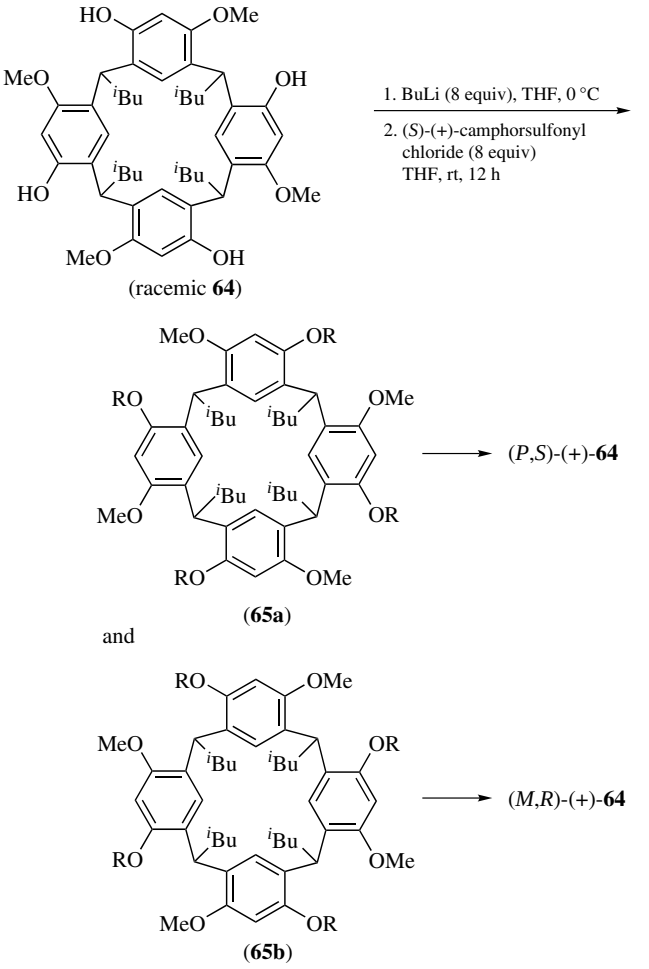


(**62**)

Synthesis of Chirally Modified Calixarenes and Resorcinarenes. (1*S*)-Camphorsulfonyl chloride was used to introduce camphorsulfonate groups to form the chirally modified calixarene **63** (eq 21)[71] and the diastereomeric tetraalkoxyresorcin[4]arenes **65** from racemic **64** (eq 22).[72] Diastereomers **65a** and **65b** can be separated chromatographically. This allowed **64** to be resolved into chiral nonracemic (*P*,*S*)-(+)-**64** and (*M*,*R*)-(−)-**64** after cleavage of the sulfonate ester groups. The absolute stereochemistry of (*P*,*S*)-(+)-**64** and (*M*,*R*)-(−)-**64** was obtained from an X-ray structure analysis of **65a**.



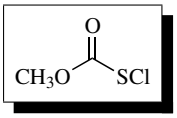
(**63**) (21)



1. Money, T., *Nat. Prod. Rep.* **1985**, *2*, 253.
2. (a) Parker, D., *Chem. Rev.* **1991**, *91*, 1441. (b) Weisman, G. R., *Asymm. Synth.* **1983**, *1*, 153.
3. Tsuchihashi, G.-I.; Mitamura, S.; Kitajima, K.; Kobayashi, K., *Tetrahedron Lett.* **1982**, *23*, 5427.
4. Oppolzer, W., *Tetrahedron* **1987**, *43*, 1969.
5. Davis, F. A.; Chen, B.-C., *Chem. Rev.* **1992**, *92*, 919.
6. Bartlett, P. D.; Knox, L. H., *Org. Synth., Coll. Vol.* **1973**, *5*, 196
7. (a) Quinkert, G.; Küber, F.; Knauf, W.; Wacker, M.; Koch, U.; Becker, H.; Nestler, H. P.; Dürner, G.; Zimmermann, G.; Bats, J. W.; Egert, E., *Helv. Chim. Acta* **1991**, *74*, 1853. (b) Quinkert, G.; Döller, U.; Eichhorn, M.; Küber, F.; Nestler, H. P.; Becker, H.; Bats, J. W.; Zimmermann, G.; Dürner, G., *Helv. Chim. Acta* **1990**, *73*, 1999. (c) Quinkert, G.; Fernholz, E.; Eckes, P.; Neumann, D.; Dürner, G., *Helv. Chim. Acta* **1989**, *72*, 1753.
8. Mori, K.; Kisida, H., *Liebigs Ann. Chem.* **1989**, 35.
9. Dehmlow, E. V.; Westerheide, R., *Synthesis* **1992**, 947.
10. Theodore, L. J.; Nelson, W. L., *J. Org. Chem.* **1987**, *52*, 1309.
11. Braun, H.; Felber, H.; Kresze, G.; Schmidtchen, F. P.; Prewo, R.; Vasella, A., *Liebigs Ann. Chem.* **1993**, 261.
12. Burke, T. R., Jr.; Nelson, W. L.; Mangion, M.; Hite, G. J.; Mokler, C. M.; Ruenitz, P. C., *J. Med. Chem.* **1980**, *23*, 1044.
13. (a) Furukawa, H.; Mori, Y.; Takeuchi, Y.; Ito, K., *J. Chromatogr.* **1977**, *136*, 428. (b) Furukawa, H.; Sakakibara, E.; Kamei, A.; Ito, K., *Chem. Pharm. Bull.* **1975**, *23*, 1625.
14. Berthet, M.; Sonveaux, E., *J. Chem. Soc., Chem. Commun.* **1983**, 10.
15. Oppolzer, W.; Chapuis, C.; Bernardinelli, G., *Tetrahedron Lett.* **1984**, *25*, 5885.
16. Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G., *Tetrahedron Lett.* **1988**, *29*, 3559.
17. Oppolzer, W.; Barras, J.-P., *Helv. Chim. Acta* **1987**, *70*, 1666.
18. Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A., *Tetrahedron Lett.* **1988**, *29*, 3555.
19. (a) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J., *J. Am. Chem. Soc.* **1988**, *110*, 8477. (b) Weismiller, M. C.; Towson, J. C.; Davis, F. A., *Org. Synth.* **1990**, *69*, 154. (c) Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Davis, F. A., *Org. Synth.* **1990**, *69*, 158.
20. *Syn* aldol: (a) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E., *J. Am. Chem. Soc.* **1990**, *112*, 2767. *Anti* aldol: (b) Oppolzer, W.; Lienard, P., *Tetrahedron Lett.* **1993**, *34*, 4321. (c) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G., *Tetrahedron Lett.* **1991**, *32*, 61.
21. Oppolzer, W.; Starkemann, C., *Tetrahedron Lett.* **1992**, *33*, 2439.
22. Eliel, E. L.; Frazee, W. J., *J. Org. Chem.* **1979**, *44*, 3598.
23. (a) Braun, H.; Felber, H.; Kresze, G.; Schmidtchen, F. P.; Prewo, R.; Vasella, A., *Liebigs Ann. Chem.* **1993**, 261. (b) Blanco, J. M.; Caamaño, O.; Eirin, A.; Fernandez, F.; Medina, L., *Bull. Soc. Chim. Belg.* **1989**, *98*, 923. (c) Caamaño, O.; Eirín, A.; Fernandez, F.; Gómez, G.; Uriarte, E., *Heterocycles* **1988**, *27*, 2839. (d) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G., *J. Org. Chem.* **1986**, *51*, 1457.
24. Halterman, R. L.; Vollhardt, K. P. C.; Welker, M. E.; Bläser, D.; Boese, R., *J. Am. Chem. Soc.* **1987**, *109*, 8105.
25. Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M., *J. Am. Chem. Soc.* **1992**, *114*, 5900.
26. Davis, F. A.; McCauley, J. P. Jr.; Chattopadhyay, S.; Harakal, M. E.; Towson, J. C.; Watson, W. H.; Tavanaiepour, I., *J. Am. Chem. Soc.* **1987**, *109*, 3370.
27. Davis, F. A.; Reddy, R. T., *J. Org. Chem.* **1992**, *57*, 2599.
28. Davis, F. A.; Chattopadhyay, S., *Tetrahedron Lett.* **1986**, *27*, 5079.
29. (a) Davis, F. A.; Wei, J.; Sheppard, A. C.; Gubernick, S., *Tetrahedron Lett.* **1987**, *28*, 5115. (b) Davis, F. A.; Lal, G. S.; Wei, J., *Tetrahedron Lett.* **1988**, *29*, 4269.
30. Davis, F. A.; Kumar, A., *J. Org. Chem.* **1992**, *57*, 3337.
31. Differding, E.; Lang, R. W., *Tetrahedron Lett.* **1988**, *29*, 6087.
32. Haslanger, M. F.; Heikes, J., *Synthesis* **1981**, 801.
33. Paulsen, H.; Brauer, O., *Chem. Ber.* **1977**, *110*, 331.
34. Woodward, R. B.; Gosteli, J.; Ernest, I.; Friary, R. J.; Nestler, G.; Raman, H.; Sitrin, R.; Suter, C.; Whitesell, J. K., *J. Am. Chem. Soc.* **1973**, *95*, 6853.
35. Ahmar, M.; Duyck, C.; Fleming, I., *J. Chem. Soc., Perkin Trans. 1* **1998**, 2721.
36. Jang, H.-Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. J., *J. Am. Chem. Soc.* **2005**, *127*, 6174.
37. Christoffers, J.; Schulze, Y.; Pickardt, J., *Tetrahedron* **2001**, *57*, 1765.
38. Alves, M. J.; Fortes, A. G.; Gonçalves, L. F., *Tetrahedron Lett.* **2003**, *44*, 6277.
39. Hall, A.; Bailey, P. D.; Rees, D. C.; Rosair, G. M.; Wightman, R. H., *J. Chem. Soc., Perkin Trans. 1* **2000**, 329.
40. Sakai, T.; Yan, F.; Kashinol, S.; Uneyama, K., *Tetrahedron* **1996**, *52*, 233.
41. Wen, J. F.; Hong, W.; Yuan, K.; Mak, T. C. W.; Wong, H. N. C., *J. Org. Chem.* **2003**, *68*, 8918.
42. (**26**) (a) Chow, H.-F.; Wan, C.-W.; Ng, M.-K., *J. Org. Chem.* **1996**, *61*, 8712. (b) Chow, H.-F.; Ng, M.-K., *Tetrahedron: Asymmetry* **1996**, *7*, 2251.

43. (**27**) (a) Tian, Y.; Chan, K. S., *Tetrahedron Lett.* **2000**, *41*, 8813. (b) Tian, Y.; Yang, Q. C.; Mak, T. C.; W.; Chan, K. S., *Tetrahedron* **2002**, *58*, 3951.
44. (**28**) Lin, L.; Zhang, A., *Tetrahedron* **2000**, *56*, 7163.
45. (**29**) Zhang, F.-J.; Lin, G.-Q., *J. Org. Chem.* **1995**, *60*, 6427.
46. (**30**) Luo, Y.; Wang, F.; Zhu, G.; Zhang, Z., *Tetrahedron: Asymmetry* **2004**, *15*, 17.
47. (**31** and **32**) Brown, R. J.; Annis, G.; Casalnuovo, A.; Chan, D.; Shapiro, R.; Marshall, W. J., *Tetrahedron* **2004**, *60*, 4361.
48. (**33**) Duan, W.; Ma, Y.; Xia, H.; Liu, X.; Ma, Q.; Sun, J., *J. Org. Chem.* **2008**, *73*, 4330.
49. King, C.-H. R.; Meckler, H.; Herr, R. J.; Trova, M. P.; Glick, S. D.; Maisonneuve, I. M., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 473.
50. Baker, L. A.; Williams, C. M.; Bernhardt, P. V.; Yanik, G. W., *Tetrahedron* **2006**, *62*, 7355.
51. Evans, P. A.; Qin, J.; Robinson, J. E.; Bazin, B., *Angew. Chem., Int. Ed.* **2007**, *46*, 7417.
52. Kaye, P. T.; Molema, W. E., *Chem. Commun.* **1998**, 2479.
53. Yeh, T.-L.; Liao, C.-C.; Uang, B.-J., *Tetrahedron* **1997**, *53*, 11141.
54. Banks, M. R.; Blake, A. J.; Cadogan, J. I. G.; Doyle, A. A.; Gosney, I., Hodgson, P. K. G.; Thorburn, P., *Tetrahedron* **1996**, *52*, 4079.
55. Shiori, T. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Winterfeld, E., eds., Pergamon: Oxford, 1991; Vol. 6, p 795.
56. Chandrasekhar, S.; Sridhar, M., *Tetrahedron: Asymmetry* **2000**, *11*, 3467.
57. Ramón, D.; J.; Yus, M., *Tetrahedron: Asymmetry* **1997**, *8*, 2479.
58. (a) Yoshioka, M.; Kawakita, T.; Ohno, M., *Tetrahedron Lett.* **1989**, *30*, 1657. (b) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M., *Tetrahedron Lett.* **1989**, *30*, 7095.
59. (a) Zhang, X.; Guo, G., *Tetrahedron Lett.* **1995**, *36*, 4947. (b) Guo, C.; Qiu, J.; Zhang, X.; Verdugo, D.; Larter, M. L.; Christie, R.; Kenney, E.; Walsh, E. J., *Tetrahedron* **1997**, *53*, 4145.
60. Qiu, J.; Guo, C.; Zhang, X., *J. Org. Chem.* **1997**, *62*, 2665.
61. Hwang, C.-D.; Uang, B.-J., *Tetrahedron: Asymmetry* **1998**, *9*, 3979.
62. Balsells, J. and Walsh, P. J., *J. Am. Chem. Soc.* **2000**, *122*, 3250.
63. Yus, M.; Ramón, D.; J.; Prieto, O., *Tetrahedron: Asymmetry* **2002**, *13*, 2291.
64. Bauer, T.; Gajewiak, J., *Tetrahedron* **2003**, *59*, 10009.
65. Yus, M.; Ramón, D.; J.; Prieto, O., *Tetrahedron: Asymmetry* **2003**, *14*, 1103.
66. Forrat, V. J.; Ramon, D. J.; Yus, M., *Tetrahedron: Asymmetry* **2005**, *16*, 3341.
67. Forrat, V. J.; Prieto, O.; Ramon, D. J.; Yus, M., *Chem. Eur. J.* **2006**, *12*, 4431.
68. Aggarwal, V. K.; Fang, G.; Kokotos, C. G.; Richardson, J.; Unthank, M. G., *Tetrahedron* **2006**, *62*, 11297.
69. Procter, D. J.; Archer, N. J.; Needham, R. A.; Bell, D.; Marchington, A. P.; Rayner, C. M., *Tetrahedron* **1999**, *55*, 9611.
70. Kawecki, R., *Tetrahedron: Asymmetry* **1999**, *10*, 4183.
71. Motta-Viola, L.; Regnouf-de-Vainsb, J.-B.; Perrin, M., *Tetrahedron Lett.* **2000**, *41*, 7023.
72. Buckley, B. R.; Page, P. C. B.; Chan, Y.; Heaney, H.; Klaes, M.; McIldowie, M. J.; McKee, V.; Mattay, J.; Mocerino, M.; Moreno, E.; Skelton, B. W.; White, A. H., *Eur. J. Org. Chem.* **2006**, 5135.

Carbomethoxysulfenyl Chloride



[26555-40-8] $C_2H_3ClO_2S$ (MW 126.56)
InChI = 1/C2H3ClO2S/c1-5-2(4)6-3/h1H3
InChIKey = TXJXPZVVSLAQOQ-UHFFFAOYAI

(peptide synthesis by prior thiol capture, solid phase peptide synthesis, thiol protective groups, formation of *S*-aryl thiocarbonates via Friedel-Crafts, preparation of unsymmetrical disulfides, formation of trisulfides)

Alternate Names: methoxycarbonylsulfenyl chloride, *S*-chloro-*O*-methylthiocarbonate.

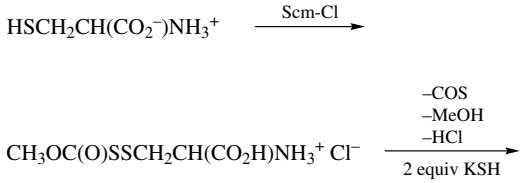
Introduction. Methoxycarbonylsulfenyl chloride (Scm-Cl),[1,2] easily prepared from equimolar amounts of methanol and chlorocarbonylsulfenyl chloride (eq 1),[2,3] finds many applications, based on the reactivity of alkoxycarbonylsulfenyl chlorides against thiols.[1] Brois and co-workers[4] realized the value of methoxycarbonylsulfenyl chloride in the synthesis of asymmetric disulfides, which led to important applications in the chemistry of cysteine and its derivatives,[5,6] particularly cysteinyl peptides.[7,8] Other applications include preparation of aromatic thiols, symmetric trisulfides, etc. The applicability of Scm-Cl surpasses its drawbacks which include relatively short storage life (1–2 months at −20 °C in sealed ampules)[9] and relatively rapid hydrolysis in the protic media that some of its most important uses require.

$$\mathrm{ClS\text{-}C(O)\text{-}Cl} \xrightarrow{\mathrm{ROH}} \mathrm{ClS\text{-}C(O)\text{-}OR} + \mathrm{RSH} \xrightarrow{0\ ^\circ\mathrm{C}} \mathrm{RSS\text{-}C(O)\text{-}OR} + \mathrm{R'SH} \longrightarrow \mathrm{RSSR'} + \mathrm{COS} + \mathrm{ROH} \quad (1)$$

Formation of Unsymmetrical Disulfides. This facile protocol (eq 1)[4,10] proceeds through sulfenyl thiocarbonate intermediates obtained in very good yields from equimolar amounts of thiols and alkoxycarbonylsulfenyl chlorides (of which methoxycarbonylsulfenyl chloride is widely used) at low temperature (generally 0–10 °C), in solvents such as methanol, chloroform, dichloromethane, and dioxane. An oxygen-free atmosphere of nitrogen is recommended.[3,11]

The thiol mediated heterolytic fragmentation of the sulfenyl thiocarbonates occurs at ambient temperature or lower, and most of the common functional groups are compatible with the procedure. The fragmentation is catalyzed by small amounts of tertiary amines (e.g., TEA).[4] Mechanistically, both cyclic and noncyclic transition states could be proposed for the fragmentation.[4]

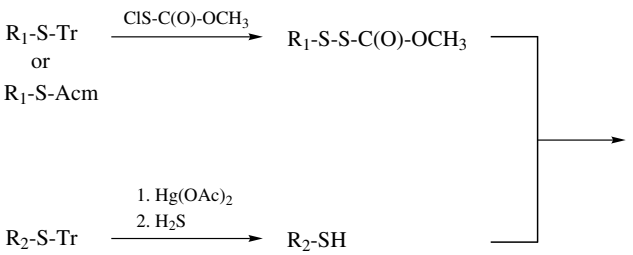
A particular case is the use of a hydrogen sulfide salt instead of the thiol, to effect the fragmentation. Treatment of the thiocarbonate derived from cysteine with 2 equiv of potassium hydrogensulfide in methanol results in the formation of the potassium salt of thiocysteine in 85% yield (eq 2).[12]



$$H_3N^+(CO_2^-)CHCH_2SS^- K^+ \quad (2)$$

When the substrate thiol is suitably substituted in such a way that a nucleophile is present in the γ position with respect to the thiol, the sulfenyl thiocarbonate intermediate derived from the thiol and Scm-Cl may cyclize in the absence of acid via intramolecular nucleophilic attack at the pre-existing thiol S (with elimination of COS and methanol). The final product forms through the intermolecular nucleophilic attack of a second thiol at the same sulfur atom, with displacement of the "internal" nucleophile.[13]

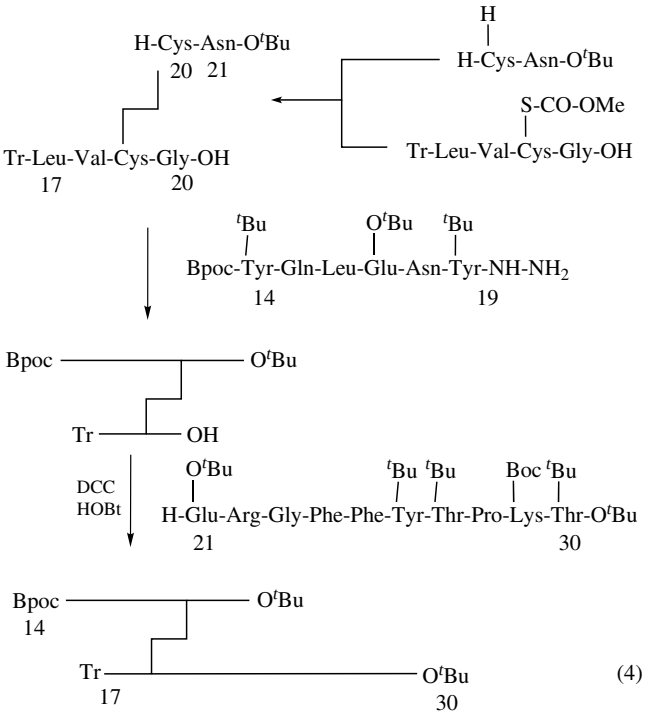
Applications of the Asymmetric Disulfides in the Chemistry of Cysteine and Cysteinyl Peptides.[14] The Brois protocol can be applied[7a] to the formation of the disulfide bridges in unsymmetrical cysteine peptides, e.g., human insulin,[7b] vasopressin, and oxytocin.[15] In the Scm method (eq 3), a substrate in which the thiol of the cysteine is protected as a trityl (Tr) or acetamidomethyl (Acm) derivative reacts with Scm-Cl to generate a sulfenyl thionocarbonate. The second thiol group, after removal of its Tr protecting group, reacts with the sulfenyl thionocarbonate to induce its fragmentation, with the corresponding formation of the asymmetric disulfide bridge.[7b]



$$R_1\text{-S-S-}R_2 + COS + ROH \quad (3)$$

This is exemplified by the construction of the disulfide bridge between A20 and B19 in human insulin (eq 4).

The reaction of cysteine hydrochloride H-Cys(H)-OH · HCl with 2 equiv Scm-Cl in methanol (1 h) provides the HCl salt of Scm-protected cysteine, H-Cys(Scm)-OH · HCl. The presence of excess HCl effectively prevents the nucleophilic attack by the amine function of cysteine to Scm-Cl; cystine is a by-product if less Scm-Cl is used.[16] The intermediate reacts with excess alkyl thiols and 1 equiv triethylamine in methanol or methanol-chloroform to afford *S*-alkylsulfenylcysteines, H-Cys(SR)-OH.[16]

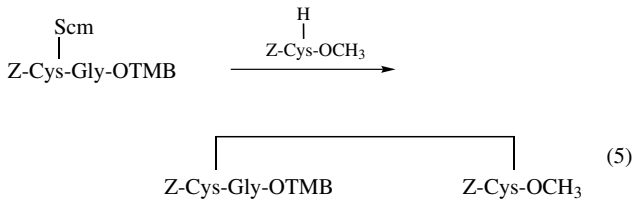


(4)

The *S*-Carbomethoxysulfenyl Group as a Protective Group for Thiols, Particularly Cysteine.[8,14] The Scm group may be used as a thiol protective group, as well as a labile intermediate in the conversion of a cysteine residue to cystine in the late stages of a peptide synthesis.[5] The crystallinity of the sulfenylthiocarbonate intermediates is an added advantage of the method, facilitating handling and purification. The S-Scm intermediates can be prepared by the reaction of Scm-Cl in methanol with thiols or with their trityl (Tr), *S*-benzhydryl (Bzh), *S*-acetamidomethyl (Acm),[17] or (in lower yield) *S*-benzyl (Bn) derivatives. When working with cysteine in its free carboxylic acid form, esterification of the carboxy group or transesterification may occur. This problem can be minimized by working at low temperature (0 °C) or by addition of calcium carbonate[5] or diethylamine[7] to the reaction mixture. Acid labile protecting groups, such as *tert*-butyl (^{t}Bu) or 2,4,6-trimethylbenzyl, are stable under the conditions of the Scm derivative formation.[5] The Scm group itself is stable to strong acids (e.g., anhydrous hydrogen fluoride and trifluoromethanesulfonic acid). The S–S bond is stable under certain peptide coupling conditions, such as DCC/NMM.[5]

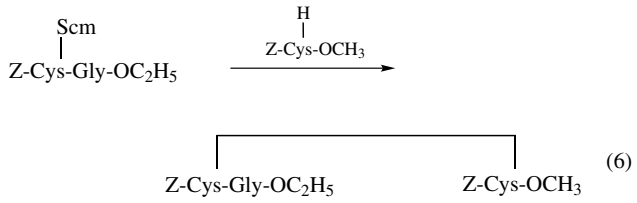
Unlike sulfenyl iodides[18] or sulfenyl thiocyanates[19] derived from cysteine compounds, which react readily with cysteine, as well as with its thioethers, hemithioacetals, and *S*-acetamidomethyl derivatives, the *S*-carbomethoxysulfenyl derivatives generate unsymmetrical disulfides only when treated with free thiols, thus are more selective in their reactivity towards sulfur nuclophiles.[5] With respect to solvents, chloroform is a frequent choice (especially in the presence of free carboxyl groups, see above). When esterification is not a concern, methanol is frequently used. Good results (79% yield) are obtained with a mixture of chloroform/methanol (1:1) for the reaction described in eq 5.[5] For the same reaction, using *N,N*-dimethylacetamide as a solvent dramatically slows down the reaction, whereas the use of dimethylformamide not only drastically reduces the product yield

but also induces the formation of large amounts of symmetric disulfide.[5]



(5)

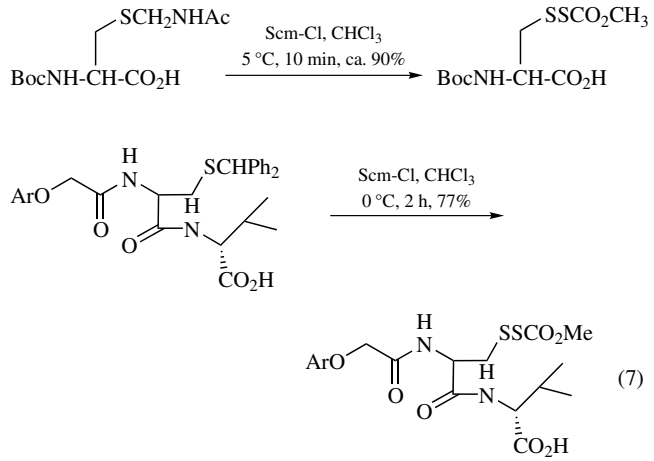
For the process described in eq 6, use of pyridine or of TFA:AcOH (1:1) as a solvent slows down the reaction and lowers the yield.[5]



(6)

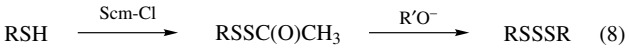
The sulfur atom in an Scm-protected thiophenol is stable to oxidation by *m*-chloroperbenzoic acid.[20]

As a transient protective group, the Scm group easily replaces the Acm group[17] or the diphenylmethyl group (eq 7).[21,22] After further manipulations of the substrate, the Scm group itself can be cleaved with dithiothreitol.[8]



(7)

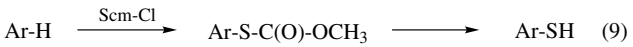
Formation of Symmetric Trisulfides via Sulfenylthiocarbonates. Treatment of a thiol with Scm-Cl followed by the decomposition of the resulting sulfenyl thiocarbonate (eq 8) with equimolar amount of alkoxide generates a symmetric trisulfide in yields that vary with the nature of the base.[23]



(8)

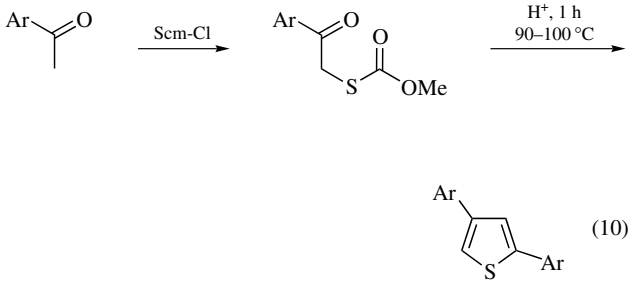
In the case of R = Et, *i*-Pr, ^{t}Bu, sodium methoxide produces ca. 1:1 trisulfide:disulfide mixture. The yield of trisulfide increases as the base is changed: ethoxide <*iso*-propoxide <*tert*-butoxide. The yield is also influenced by the nature/bulkiness of the alkyl R in the alkylsulfenyl group (Me < Et < Pr < *i*-Pr < ^{t}Bu < Ph). Attempts to prepare monomeric cyclic trisulfides starting from bis(sulfenyl) thiocarbonates were unsuccessful, resulting instead in the formation of various bis(trisulfide) macrocycles, accompanied by variable but significant amounts of polymers.[24] Work in acidic media (pH 2) facilitates trisulfide formation.[25]

Preparation of Aromatic Thiols. Reaction of methoxycarbonylsulfenyl chloride with benzene and substituted benzenes in the presence of Lewis acids ($AlCl_3$, BF_3) in dichloromethane, carbon disulfide, or excess substrate as a solvent generates aryl thiocarbonates in low to good yields. Hydrolysis of the aryl thiocarbonates with aqueous methanolic potassium hydroxide generates the corresponding thiophenols in high yield (eq 9).[26]



(9)

Preparation of Diarylthiophenes. Reaction of acetophenones, under acidic conditions, with Scm-Cl generates 2-oxoalkylthiocarbonates in 60–80% yield. These, in turn, when heated to ca. 100 °C in the presence of sulfuric acid, produce 2,5-diarylthiophenes in 40–74% yield (eq 10).[26]

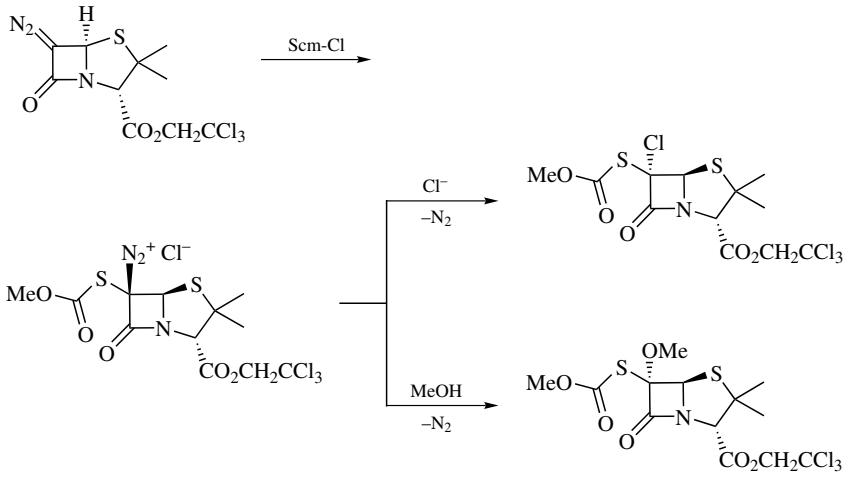


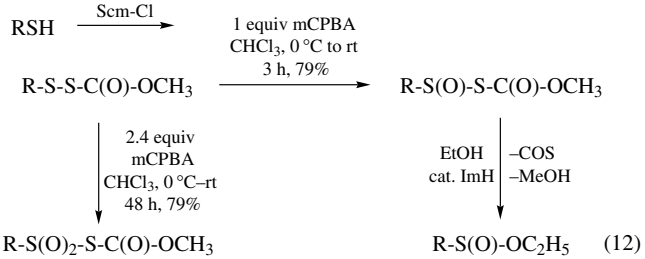
(10)

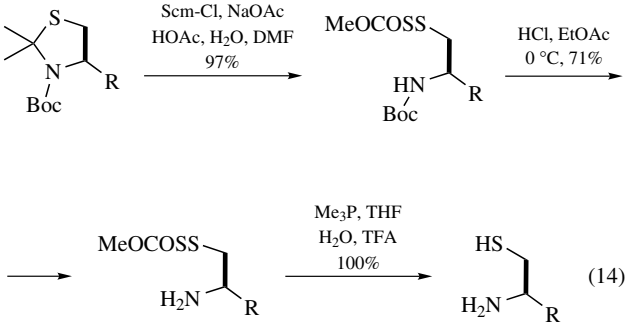
The yield of the last step appears to be favorably influenced by the presence of electron-donating groups (*p*-Me >> *p*-Br > H).[26]

Reaction with Diazo Compounds. Treatment of a diazolactam derived from penicillin with Scm-Cl in dichloromethane containing an excess of methanol gives a 6α-methoxy-6-methoxycarbothio derivative in 78% yield, accompanied by 3% of the corresponding 6α-chloro-6-methoxycarbothio derivative.[27] When the reaction is run in the absence of methanol, the 6α-chloro derivative is obtained in 88% yield. The reaction proceeds via a common diazonium intermediate (eq 11).[27]

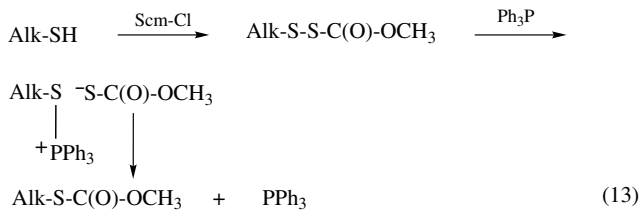
Preparation of Sulfinyl and Sulfonyl Thiocarbonates. Treatment of the sulfenyl thiocarbonates formed from thiols and Scm-Cl with an equimolar amount of *m*-chloroperbenzoic acid in chloroform generates the corresponding sulfinyl thiocarbonate which, unlike its precursor, is reactive towards ethanol in the presence of catalytic amount of imidazole.[28] The latter reaction also establishes the regiospecificity of the oxidation reaction. The oxidation of the same sulfenyl thiocarbonate substrate with excess *m*CPBA (min. 2.4 mol *m*CPBA/mol substrate) produces the corresponding sulfonyl thiocarbonate (eq 12).[28]







Desulfurization of Alkylsulfenyl Methyl Thiocarbonates. Treatment of alkylsulfenyl methyl thiocarbonates derived from alkyl thiols and Scm-Cl with triphenylphosphine at 0 °C in benzene generates *S*-alkyl methyl thiocarbonates in good yield (78% for alkyl = benzyl) (eq 13).[29] Arylsulfenyl methyl thiocarbonates do not parallel this behavior vs. triphenylphosphine[29] but they react cleanly with tributylphosphine (e.g., in dioxane-water) to generate the free arylthiol (see below).[30] The reductive cleavage of alkylsulfenyl methyl thiocarbonates with trialkylphosphines (Me_3P, Et_3P, Bu_3P) can be achieved with practically quantitative yields in protic solvents (THF-water) in the presence of acids (TFA).[30–32]



In eq 14, a Boc-protected dimethylketal derivative of cysteine is first cleaved with Scm-Cl, in acetate buffer. The resulting intermediate has the amino function Boc-protected and the thiol function Scm-protected. Acidic cleavage of the Boc group followed by reductive cleavage of the sulfenyl thiocarbonate with trimethylphosphine in aq THF in the presence of trifluoroacetic acid frees both functionalities.[31–33]

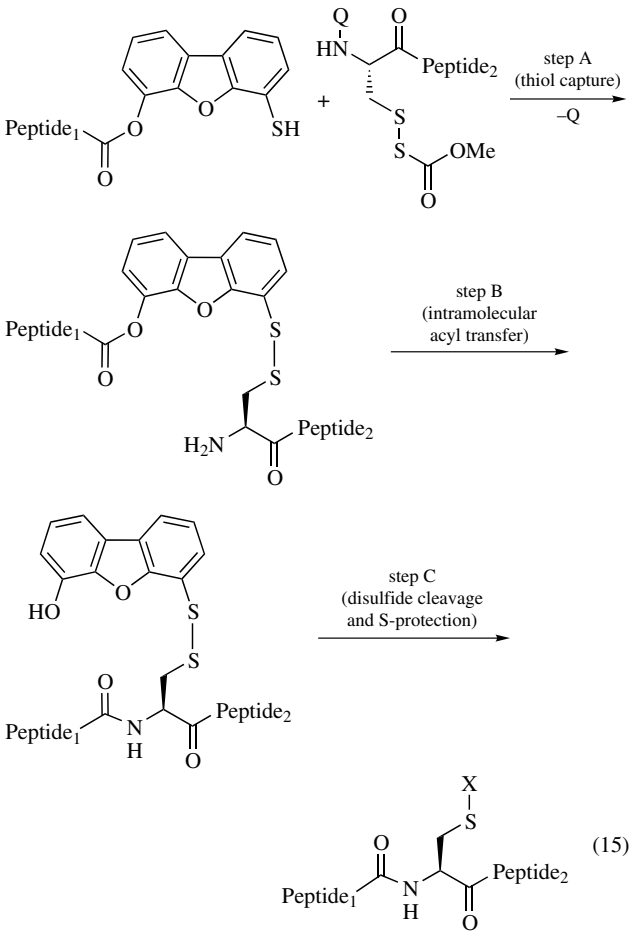
Peptide Synthesis by Prior Thiol Capture. A coupling method has been designed to be used at the late stages of fragment condensation syntheses of large peptides that contain cysteine residues spaced 5–20 amino acid residues apart.[6,30] The method takes advantage of an N-terminal cysteine residue and centers around a 6-hydroxy-4-mercaptodibenzofuran template that puts the participating fragments in the right proximity, with the right orientation. Other templates examined for the same process were not as successful.[34,35] The 4-mercapto functionality is used to form an unsymmetric disulfide with the cysteine residue via the Brois protocol involving Scm-Cl as described above (eq 1). The fragments containing the template are first prepared by solid-phase synthesis and purified. They are then linked together in a three-step sequence known as the "thiol capture strategy" (eq 15).[6,30]

Step A involves disulfide bond formation between a peptide fragment derivatized at the C-terminus as 4-acyloxy-6-mercaptodibenzofuran and a peptide fragment bearing an S-Scm activated cysteine residue at its *N*-terminus. This step was designed to occur cleanly and very rapidly at submillimolar concentrations in protic solvents or solvent mixtures. The intramolecular acyl transfer (step B) is highly efficient (effective molarity > 1 M),[35,36] to the effect that, for most cases, a very weakly activated phenolic ester can be employed and many quite reactive side-chain functions in R and R′ can be left unprotected.[30] These high reactivity criteria are met best in the protein-solubilizing solvent hexafluoro-2-propanol (HFIP) and its mixtures with water and acetonitrile.[6]

The use of a phenolic ester as anchoring group limits the choice of the protective groups. An appropriate choice is *tert*-butyloxycarbonyl (Boc, trifluoroacetic acid cleavable) for N^{α}-blocking of the amino acid esterified with the phenol and functionalized

benzyl groups for side-chain functions.[30] Alternatives include *tert*-butyl-derived side-chain blocking groups and 2-*p*-biphenylyl-2-propyloxycarbonyl (Bpoc) for N^{α}-protection.[6]

The resin-bound fragment preparation starts with the chlorine displacement from the chloromethylene function on a chloromethylated polystyrene by the cesium salt of *Z*-L-Cys(Tr)-OH. The resulting benzyl ester is treated with Scm-Cl to form the active intermediate sulfenyl thiocarbonate which is allowed to react with 4-acyloxy-6-mercaptodibenzofuran, preferably in dichloromethane–hexafluoro-2-propanol, with or without catalytic triethylamine (eq 16).[30]

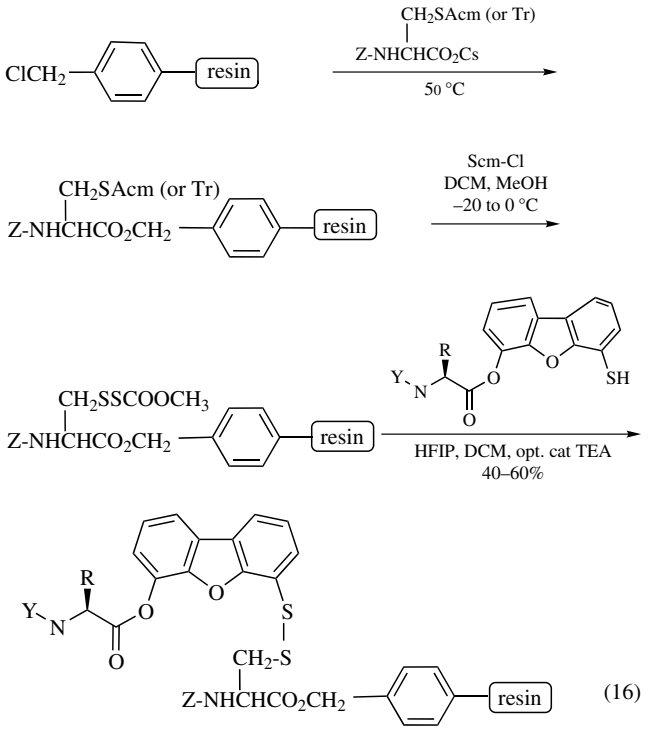


X = acetyl, 2,4-dinitrophenyl

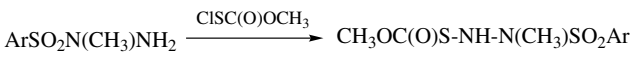
An alternative to Acm and Tr for the temporary protection of cysteine is 2,2-dimethylthiazolidine-4-carboxylic acid (H-Dmt-OH, used as the anhydride derived from Boc-Dmt-OH or as Boc-Dmt-OPfp).[9]

It is often simpler to modify the sequence in eq 16 to a sequence in which the resin-bound sulfenyl thiocarbonate intermediate is first reacted with 4-hydroxy-6-mercaptodibenzofuran. The free phenol is then acylated by 3–4 equiv of a symmetrical anhydride derived from an N^{α}-carbamate-blocked amino acid, in the presence of diisopropylethylamine in dichloromethane (ca. 10–30 min reaction time at 0 °C).

The reductive cleavage of the disulfide bond (eq 15, step C) can be performed cleanly and with high reaction rates (almost instantaneously) by treatment with 1 equiv of tributylphosphine in dioxane-water at room temperature.[30]

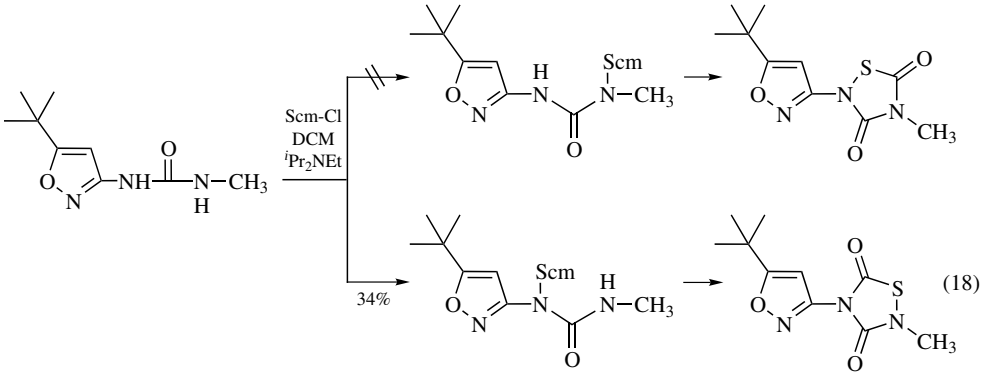


Reaction with Nitrogen Nucleophiles. The reaction of Scm-Cl with arylsulfonylhydrazines (or aralkylsulfonylhydrazines) occurs in minutes at 0 °C in anhydrous ether to provide stable, recrystallizable products (eq 17).[37]

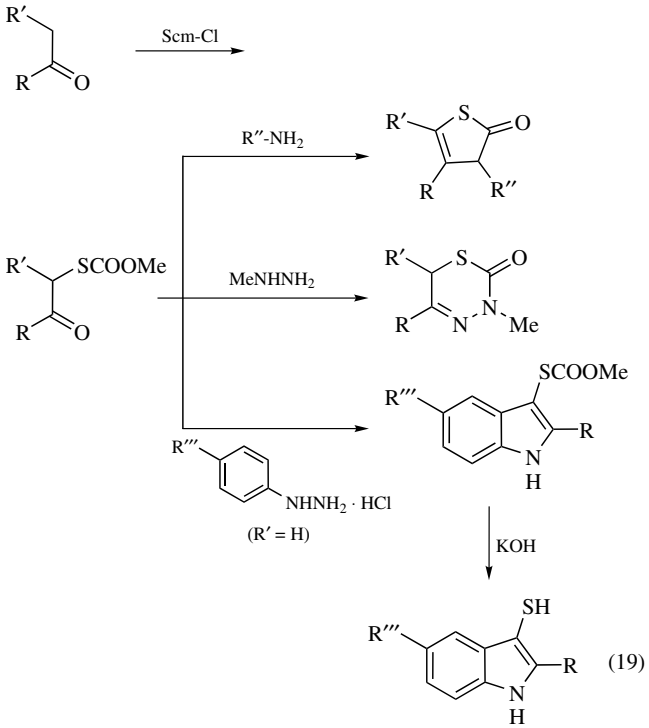


The relatively high reactivity of Scm-Cl, however, lowers the selectivity towards substrates with more than one nitrogen nucleophile.[38] Nevertheless, with less reactive nucleophiles, such as the two nitrogens in unsymmetrically substituted ureas, selectivity is possible. In the reaction shown in eq 18, only the nitrogen adjacent to the oxazole ring reacts with the electrophile Scm-Cl (albeit in low yield, 34%).[39]

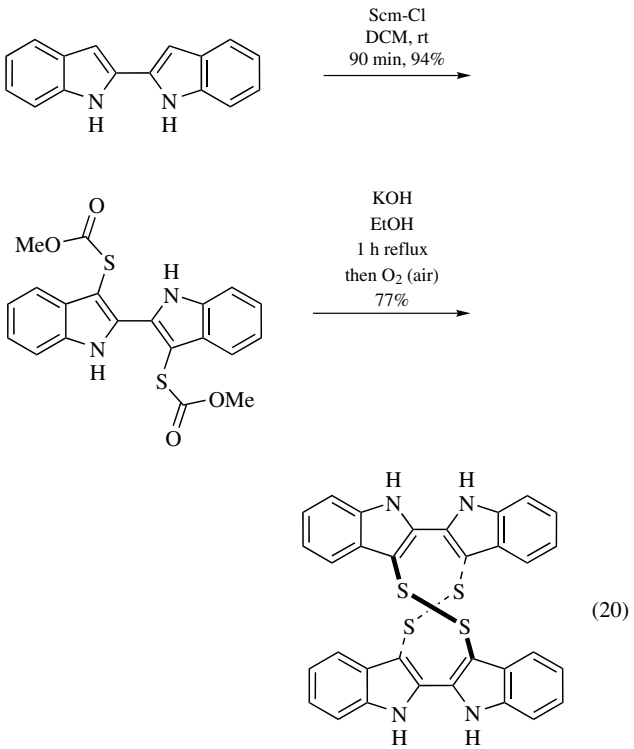
α-Methoxycarbonylsulfenylation of Carbonyl Compounds as a Route to Heterocycles. Ketones and aldehydes react with equimolar amounts of Scm-Cl in chloroform to form, in moderate to good yields, α-methoxycarbonylsulfenyl ketones or aldehydes that, upon condensation with amines, alkylhydrazines, or arylhydrazines afford, respectively, thiazolones, thiadiazinones, and 3-indolethiols (eq 19).[40]



(18)



(19)

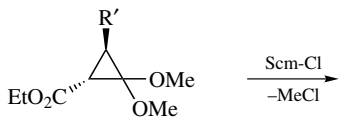


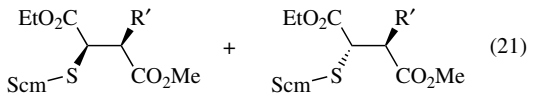
(20)

In more complex substrates, the regio- and stereoselectivity of the reaction of Scm-Cl with carbon nucleophiles may be hard to predict.[41]

Other Heterocycles. Reaction of 2,2′-biindolyl in dichloromethane with 2 equiv Scm-Cl generates a 3,3′-bis(methoxycarbonylsulfenyl) derivative that, upon heating with base and exposure to air, produces a highly insoluble bis-disulfide "dimer" (eq 20).[42]

Other Reactions. The ring opening of the functionalized 2-alkyl-3-ethoxycarbonyl-1,1-dimethoxypropanes in eq 21 with 1 equiv Scm-Cl in carbon tetrachloride generates the corresponding *syn*- and *anti*-2-sulfenylbutanedioates in low to fair yields, with 70–80% de in favor of the *syn* isomer. When the alkyl substituent in the substrate is replaced by hydrogen, the reaction takes a different pathway.[43]





(21)

syn *anti*

Related Reagents. Benzenesulfenyl Chloride; 2-(Methylthio)-1*H*-isoindole-1,3(2*H*)-dione; *N*-*tert*-Butylthiophthalimide; *N*-Phenylthiophthalimide; Dimethyl(methylthio)sulfonium Tetrafluoroborate; Ethyl Thiosulfinate; Disulfur Dichloride.

1. Bohme, H.; Steudel, H.-P., *Liebigs Ann. Chem.* **1969**, *730*, 121.
2. Zumach, G.; Kühle, E., *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 54 and references therein.
3. Barany, G.; Schroll, A. L.; Mott, A. W.; Halsrud, D. A., *J. Org. Chem.* **1983**, *48*, 4750.
4. Brois, S. J.; Pilot, J. F.; Barnum, H. W., *J. Am. Chem. Soc.* **1970**, *92*, 7629.
5. Hiskey, R. G.; Muthukumaraswamy, N.; Vunnam, R. R., *J. Org. Chem.* **1975**, *40*, 950.
6. Fotouhi, N.; Galakatos, N. G.; Kemp, D. S., *J. Org. Chem.* **1989**, *54*, 2803.
7. (a) Kamber, B., *Helv. Chim. Acta* **1973**, *56*, 1370. (b) Kamber, B., *Z. Naturforsch.* **1981**, *36b*, 508.
8. Greene, T. W.; Wuts, P. G., *Protective Groups in Organic Chemistry*, 2nd ed.; Wiley: Chichester, 1991, p 303.
9. Kemp, D. S.; Carey, R. I., *J. Org. Chem.* **1989**, *54*, 3640.
10. Field, L.; Ravichandran, R., *J. Org. Chem.* **1979**, *44*, 2624.
11. Brasili, L.; Giannella, M.; Melchiorre, C.; Belleau, B.; Benfey, B. G., *Eur. J. Med. Chem.* **1981**, *16*, 115.
12. Smith, D. J.; Venkatraghavan, V., *Synth. Commun.* **1985**, *15*, 945.
13. Sanchez, J. P., *J. Heterocyl. Chem.* **1997**, *34*, 1463.
14. Barany, G.; Kneib-Cordonnier, N.; Mullen, D. G., *Int. J. Peptide Protein Res.* **1987**, *30*, 705.
15. van Nispen, J. W.; Hannink, J. A. J.; Schoffelmeer, M. S.; Janssen, W. P. A.; Polderdijk, J. P.; Greven, H. M., *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 68.
16. Rietman, B. H.; Peters, R. F. R.; Tesser, G. I., *Synth. Commun.* **1994**, *24*, 1323.
17. Schroll, A. L.; Barany, G., *J. Org. Chem.* **1989**, *54*, 244.
18. Kamber, B., *Helv. Chim. Acta* **1971**, *54*, 927.
19. Hiskey, R. G.; Ward, B. F., *J. Org. Chem.* **1970**, *35*, 1118.
20. Kemp, D. S.; Buckler, D. R., *J. Org. Chem.* **1989**, *54*, 3647.
21. Baldwin, J. E.; Pratt, A. J.; Moloney, M. G., *Tetrahedron* **1987**, *43*, 2565.
22. Baldwin, J. E.; Jesudason, C. D.; Moloney, M. G.; Morgan, D. R.; Pratt, A. J., *Tetrahedron* **1991**, *47*, 5603.
23. Harpp, D. N.; Granata, A., *Tetrahedron Lett.* **1976**, 3001.
24. Harpp, D. N.; Granata, A., *J. Org. Chem.* **1979**, *44*, 4144.
25. Chen, L.; Zoulikova, I.; Slaninova, J.; Barany, G., *J. Med. Chem.* **1997**, *40*, 864.
26. Schroth, W.; Hassfeld, M.; Schiedewitz, W.; P fotenhauer, C., *Z. Chem.* **1977**, *17*, 411.
27. Sheehan, J. C.; Commons, T. J., *J. Org. Chem.* **1978**, *43*, 2203.
28. Harpp, D. N.; Granata, A., *Synthesis* **1978**, 782.
29. Harpp, D. N.; Granata, A., *J. Org. Chem.* **1980**, *45*, 271.
30. Kemp, D. S.; Galakatos, N. G., *J. Org. Chem.* **1986**, *51*, 1821, and references therein.
31. Yang, H.; Sheng, X. C.; Harrington, E. M.; Ackermann, K.; Garcia, A. M.; Lewis, M. D., *J. Org. Chem.* **1999**, *64*, 242.
32. O'Connell, C. E.; Ackermann, K.; Rowell, C. A.; Garcia, A. M.; Lewis, M. D.; Schwartz, C. E., *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2095.
33. O'Connell, C. E.; Rowell, C. A.; Ackermann, K.; Garcia, A. M.; Lewis, M. D.; Kowalczyk, J., *Chem. Pharm. Bull.* **2000**, *48*, 740.
34. Kemp, D. S.; Galakatos, N. G., Bowen, B.; Tan, K. *J. Org. Chem.* **1986**, *51*, 1829.
35. Kemp, D. S.; Carey, R. I.; Dewan, J. C.; Galakatos, N. G.; Kerkman, D.; Leung, S.-L., *J. Org. Chem.* **1989**, *54*, 1589.
36. Kemp, D. S.; Carey, R. I., *J. Org. Chem.* **1993**, *58*, 2216.
37. Hrubiec, R. T.; Shyam, K.; Cosby, L. A.; Sartorelli, A. C., *J. Med. Chem.* **1986**, *29*, 1777.
38. Pilgram, K. H.; Gale, L. H., *J. Heterocycl. Chem.* **1988**, *25*, 193.
39. Pilgram, K. H.; Gale, L. H., *J. Heterocycl. Chem.* **1988**, *25*, 607.
40. Sanemitsu, Y.; Kawamura, S.; Tanabe, Y., *J. Org. Chem.* **1992**, *57*, 1053.
41. Kozikowski, A. P.; Campiani, G.; Tückmantel, W., *Heterocycles* **1994**, *39*, 101.
42. Janosik, T.; Bergman, J.; Romero, I.; Stensland, B.; Stalhandske, C.; Marques, M. M. B.; Santos, M. M. M.; Lobo, A. M.; Prabhakar, S.; Duarte, F. M.; Florencio, M. H., *Eur. J. Org. Chem.* **2002**, 1392.
43. Graziano, M. L.; Iesce, M. R.; Cermola, F., *Synthesis* **1999**, 1944.

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Carbon Disulfide[1]

[75-15-0] CS_2 (MW 76.14)
InChI = 1/CS2/c2-1-3
InChIKey = QGJOPFRUJISHPQ-UHFFFAOYAS

(starting material for the synthesis of various sulfur and heterocyclic compounds;[1] protecting group for secondary amines[2])

Physical Data: mp −111.6 °C; bp 46.3 °C; *d* 1.26 g cm^{-3}; flash-point −30 °C; fire point 102 °C.

Solubility: sol alcohol, ether, THF, benzene, CCl_4, $CHCl_3$; insol cold H_2O.

Form Supplied in: colorless liquid; discolors to yellow under influence of light.

Handling, Storage, and Precautions: should be stored in brown bottles in absence of light. CS_2 forms explosive mixtures with air (explosion limit 1–60 vol %). CS_2 is teratogenic. Constant inhalation or constant resorption through the skin cause chronic symptoms of poisoning, e.g. sight defects and headache. Inhalation of concentrated CS_2 vapor can be lethal. Use in a fume hood.

Original Commentary

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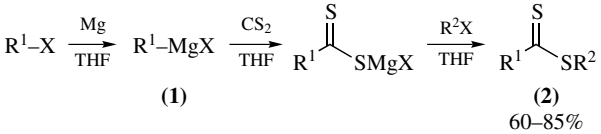
Reactions with Organometallic Compounds.

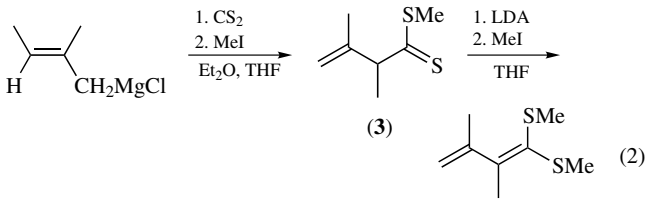
Grignard Reagents. Treatment of CS_2 with Grignard reagents RMgX (**1**) leads to dithioesters (**2**) (eq 1).



(1)

If THF is used as solvent, dithioesters can be obtained in 60–85% yield.[3] This method fails when *t*-alkyl- or cyclohexylmagnesium halides are used. With diethyl ether as solvent, the dithioesters are obtained in poor yields.[4] The reaction of CS_2 with an allylic Grignard reagent followed by methylation affords

the dithioesters (**3**), bearing an inverted allylic chain as expected.[5] Treatment of (**3**) with first lithium diisopropylamide, then with iodomethane, leads to an isoprenic ketene dithioacetal (**4**) (eq 2).

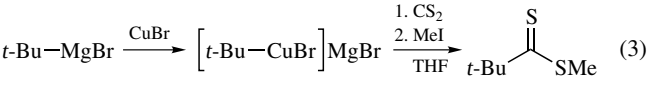


(**3**) (2)

(**4**) 83%

It is also possible to prepare various ketene dithioacetals in a one-pot synthesis with Grignard reagents and CS_2 as starting materials.[6]

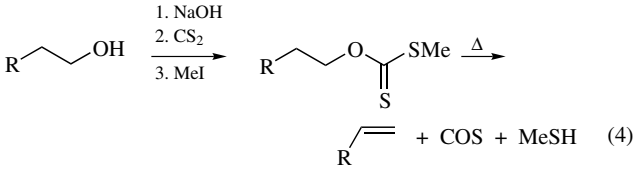
Organocopper Reagents. When catalytic amounts of copper(I) bromide are used, the reaction of CS_2 with Grignard reagents leads to dithioesters in 80–100% yield (eq 3).[7]



(**5**) 95% (3)

The organocopper(I) compound (**5**) is the reacting species.[7a] With this method, halides containing bulky groups can also be converted to dithioesters.

Reactions with Alcohols. Treatment of alcohols with sodium hydroxide and CS_2 and subsequent reaction with an alkyl halide, usually methyl iodide, leads to *O*-alkyl *S*-methyl dithiocarbonates which can be pyrolyzed to alkenes (Tschugaeff reaction) (eq 4).[8]



(4)

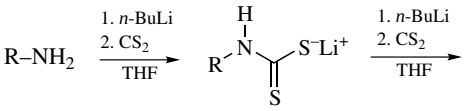
Formation of the metal salt of the alcohol can be difficult.[9] If sodium methylsulfinylmethylide in DMSO is used as base, the dithiocarbonates can be prepared in good yields.[10] The decomposition temperature is lowered when pyrolysis is also carried out in DMSO.[11]

Vicinal diols react with CS_2 under basic conditions, to give the corresponding bis-dithiocarbonates. Reduction with tributyltin hydride in toluene[12] gives high yields of the alkenes.

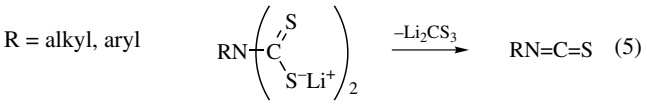
Recently, a variety of reducing agents has been developed to convert dithiocarbonates derived from alcohols, especially secondary ones, to alkanes. The hydroxy function can be selectively replaced by hydrogen under mild conditions, with tri-*n*-butylstannane,[13a] tri-*n*-butylstannane/triethylborane,[13b] or tris(trimethylsilyl)silane/azobisisobutyronitrile[13c] as radical-based reducing agents.

Reaction with Amines.

Primary Amines. Treatment of primary amines with base and CS_2 leads to isothiocyanates via the dithiocarbamate derivatives.[14] Alkyl or aryl amines which do not contain groups that react with butyllithium, can be converted in 55–99% yield to the corresponding isothiocyanates. The amines are treated with an equimolar amount of butyllithium and CS_2 to give the lithium dithiocarbamate (**6**) Subsequent reaction with *n*-butyllithium and CS_2 forms the complex (**7**). Loss of Li_2CS_3 leads to an isocyanate (eq 5).[15]

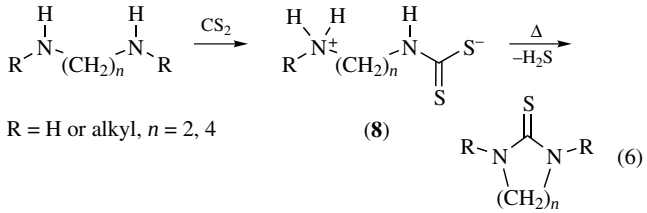


(**6**)



(**7**) 75–99% (5)

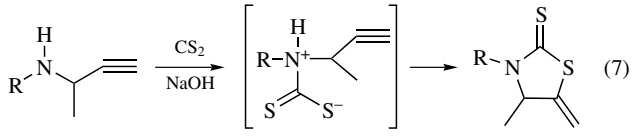
Diamines. Aliphatic diamines react with CS_2 to give betaines (**8**). After pyrolysis of (**8**), cyclic thiourea derivatives are obtained (eq 6).[16]



55–95% (6)

In the same way, 1,2-diarylamines and their hetero analogs can be converted to heterocyclic compounds.[17]

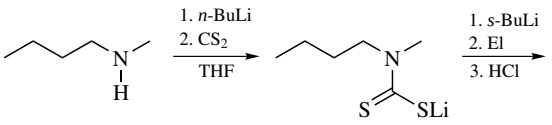
Secondary Amines. Treatment of secondary amines with base and CS_2 leads to the corresponding dithiocarbamates.[18] Dithiocarbamates of functionalized secondary amines form heterocyclic compounds.[19] For example, monoalkylaminobutynes (**9**) react readily with CS_2 to give 4-methyl-3-alkyl-5-methylenethiazolidine-2-thiones (**10**) (eq 7).[20]



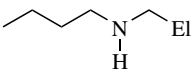
(**9**)
R = alkyl, benzyl

(**10**)
58–87% (7)

Protecting Group. As mentioned above, under basic conditions, secondary amines form with CS_2 dithiocarbamates. Subsequent reaction with an organometallic base and one equivalent of electrophile gives, in good yields, the secondary amines substituted in the α-position (eq 8).[2,21]



Electrophile (El) = alkyl halogenides, carbonyl compounds



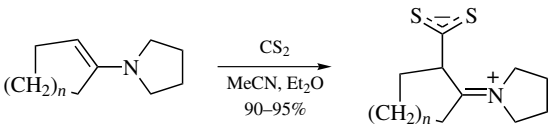
(8)

68–87%

The natural reactivity at α-position is umpoled.[22] This is a simple and versatile method for nucleophilic aminoalkylation[23] in a one-pot procedure. The reaction can be applied to numerous aliphatic and aromatic secondary amines.

Reactions with Enolizable Hydrogen Compounds.

Enamines. Reactions of enamines with CS_2 afford several heterocycles.[24] Treatment of cyclic enamines with CS_2 leads to 1,4-dipoles (**11**) (eq 9).



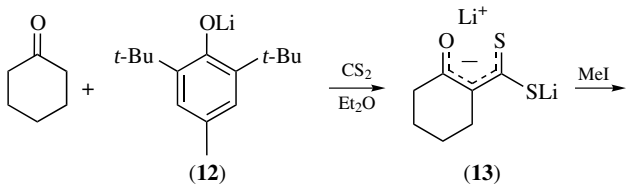
(9)

n = 1, 2, 3

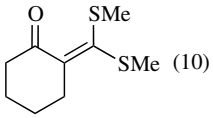
(11)

In the absence of moisture the 1,4-dipoles (**11**) can be stored for several days at 0 °C. Further reactions with electrophiles lead to various heterocycles.[25]

Carbonyl Compounds. In the case of aldehydes, only self-condensation products are obtained, whereas aliphatic ketones usually form the corresponding dithiocarboxylates or α-ketoketene dithioacetals.[26] If cyclic ketones are used, occurrence of carbon–carbon cleavage or formation of α-ketoketene acetals depend on the steric demands of the base. Treatment of cyclohexanone with lithium 4-methyl-2,6-di-*t*-butylphenoxide (**12**) (readily obtained by treatment of the phenol with *n*-butyllithium) and CS_2, followed by methylation, leads via the dithiocarboxylate ion (**13**) to the α-ketoketene dithioacetal (**14**) (eq 10).[27]



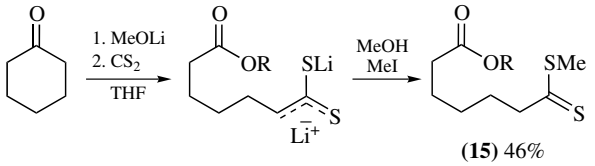
(12) **(13)**



(10)

(14) 86%

If the reaction is carried out with lithium methoxide as base, 1,1-dithiodicarboxylic acid ester (**15**) is formed (eq 11).[28]



(11)

(15) 46%

This carbon–carbon cleavage in cyclic ketones corresponds to an inverse Dieckmann-type reaction. Bulkier alkoxides like ethoxide or isopropoxide afford only α-ketoketene dithioacetals.[27]

First Update

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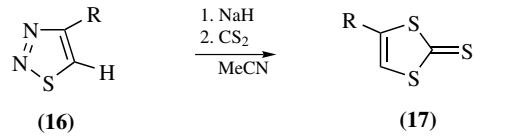
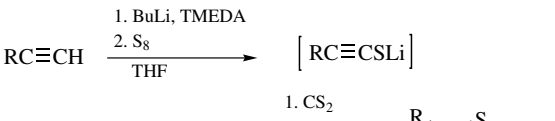
Reactions with Thiolates and Selenolates.

Alkynethiolates and Selenolates. Sodium alkynethiolates are generated from 1,2,3-thiadiazoles (**16**) and reacted with CS_2. Nucleophilic attack of sodium alkynethiolates to CS_2 followed by the intramolecular cyclization proceeded to give 1,3-dithiole-2-thiones (**17**) in 57–98% yields (eq 12).[29] Lithium alkynethiolates, which are derived from terminal acetylenes, BuLi, TMEDA, and elemental sulfur, can also be used in this cyclization reaction (eq 13).[30] In the case of the lithium salts, CS_2 is added at −90 °C, and the reaction mixture is quenched by adding water containing THF at this temperature to lead to (**17**). Lithium alkyneselenolates participate in this type of transformation (eq 14).[31,32] The reaction mixture is quenched with alkyl thiocyanates or a combination of elemental selenium and alkyl iodides to give 1,3-selenothiole-2-thiones (**18**) in 80–98% yields. The reaction is quenched in a similar manner to that from the lithium alkynethiolates.[32]



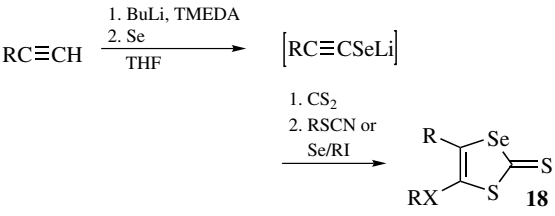
(12)

(16) **(17)**



(13)

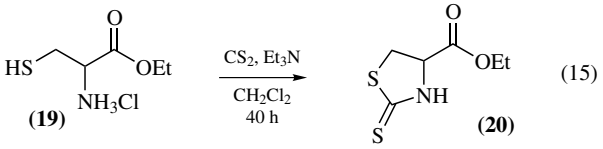
(17)



(14)

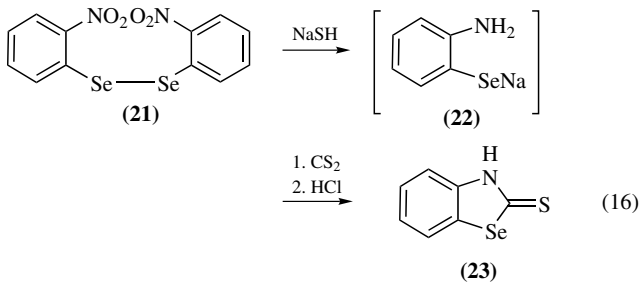
X = S, Se

Aminothiolate. The treatment of 1,2-aminothiol salt (**19**) with CS_2 in the presence of Et_3N leads to thiazoline (**20**) (eq 15).[33]



(15)

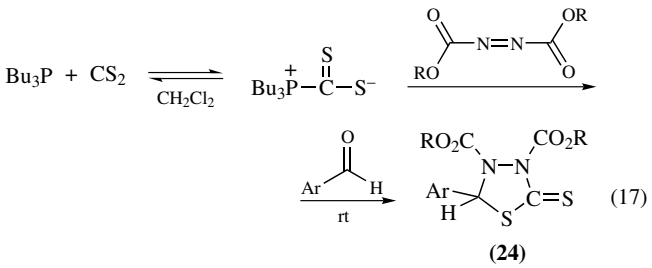
Aminoselenolate. Bis(*O*-nitrophenyl) diselenide (**21**) is reduced with sodium hydrosulfide to generate *O*-aminobenzeneselenolate (**22**) as a presumed intermediate. Then, (**22**) is reacted with CS_2 followed by the acidic workup to give the benzeneselenazole-2-thione (**23**) in 90% yield (eq 16).[34]



(16)

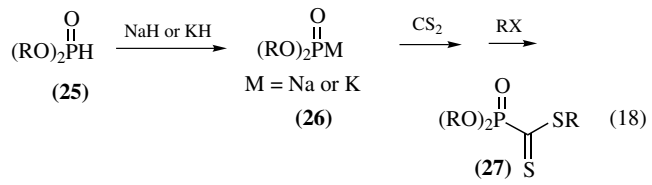
Reactions with Phosphorus-containing Nucleophiles.

Tributylphosphine. The adduct between Bu_3P and CS_2 is readily formed in CH_2Cl_2, and reacts with dialkyl azodicarboxylates and aldehydes to give 1,3,4-thiadiazolidine-2-thiones (**24**) in 36–86% yields (eq 17).[35]



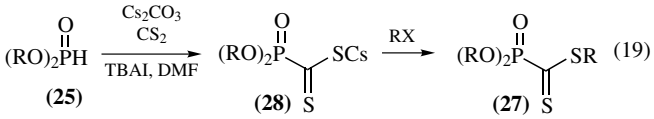
(17)

Phosphites. The deprotonation of *O*,*O*-dialkyl phosphites (**25**) with KH[36] or NaH[37] generates metal phosphites (**26**), which can be reacted with CS_2 followed by the reaction with alkyl halides to afford *O*,*O*-dialkyl phosphonodithioformates (**27**) (eq 18). The deprotonation with KH is carried out at 0 °C for 3 h, whereas the reaction with NaH is performed in THF at reflux for 5 min. As alkyl halides, methyl iodide, trityl, fluorenyl, and benzyl bromides are used, and the products (**27**) are obtained in 65–85% yields.



(18)

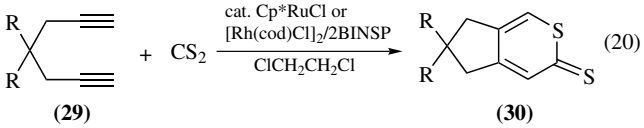
As an improved method, the combination of cesium carbonate and tetrabutylammonium iodide (TBAI) is used as a base in DMF (eq 19).[38] The cesium salts (**28**) are formed by treating (**25**) with Cs_2CO_3 and TBAI at 23 °C for 1 h. The use of other alkali metal carbonates gives the corresponding salts in lower yields on the basis of their trapping with benzyl bromide. TBAI is also crucial in the reaction. The reaction in the absence of TBAI is less effective. A variety of alkyl halides such as primary and secondary alkyl bromides are used for the alkylation of the salts (**28**). With isoleucine bromide as electrophile, the nucleophilic substitution reaction with the salt (**28**) proceeds with retention of configuration.



(19)

Reactions with 1,6-Diynes.

[2 + 2 + 2] Cycloadditions. Cp*RuCl-catalyzed [2 + 2 + 2] cycloaddition of 1,6-dinyne (**29**) with CS_2 in $ClCH_2CH_2Cl$ proceeds at 90 °C for 6 h to give dithiopyrone (**30**) in 54% yield (eq 20).[39] The use of the combination of $[Rh(cod)Cl]_2$ and BINAP at 80 °C gave dithiopyrone (**30**) in better yields, although longer reaction times are necessary.[40]



(20)

1. (a) Yokoyama, M.; Imamoto, T., *Synthesis* **1984**, 797. (b) Thömel, v. F., *Chem.-Ztg.* **1987**, *111*, 285. (c) Tominaga, Y., *J. Heterocycl. Chem.* **1989**, *26*, 1167.
2. Ahlbrecht, H.; Schmitt, C.; Kornetzky, D., *Synthesis* **1991**, 637.
3. (a) Meijer, J.; Vermeer, P.; Brandsma, L., *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 601. (b) Boudin, A.; Cerveau, G.; Chuit, C.; Corriu, R. J. P.; Reye, C., *Tetrahedron* **1989**, *45*, 171.
4. (a) Houben, J.; Schultze, K. M. L., *Chem. Ber.* **1911**, *44*, 3226. (b) Mayer, R.; Scheithauer, S.; Kunz, D., *Chem. Ber.* **1966**, *99*, 1393.
5. Cazes, B.; Julia, S., *Tetrahedron Lett.* **1978**, *42*, 4065.
6. Kaya, R.; Beller, N. R., *Synthesis* **1981**, 814.
7. (a) Westmijze, H.; Kleijn, H.; Meijer, J.; Vermeer, P., *Synthesis* **1979**, 432. (b) Camus, A.; Marsich, N.; Nardin, G., *J. Organomet. Chem.* **1980**, *188*, 389. (c) Verkruijsse, H. D.; Brandsma, L., *J. Organomet. Chem.* **1987**, *332*, 95.
8. Nace, H. R., *Org. React.* **1962**, *12*, 57.
9. de Groot, A.; Evenhuis, B.; Wynberg, H., *J. Org. Chem.* **1968**, *33*, 2214.
10. (a) Corey, E. J.; Chaykovsky, M., *J. Am. Chem. Soc.* **1965**, *87*, 1345. (b) Sjöberg, K., *Tetrahedron Lett.* **1966**, 6383.
11. Meurling, P.; Sjöberg, K.; Sjöberg, B., *Acta Chem. Scand.* **1972**, *26*, 279.
12. Barrett, A. G. M.; Barton, D. H. R.; Bielski, R., *J. Chem. Soc., Perkin Trans. 1* **1979**, 2378.
13. (a) Barton, D. H. R.; McCombie, S. W., *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Nozaki, K.; Oshima, K.; Utimoto, K., *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2578. (c) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B., *J. Org. Chem.* **1991**, *56*, 678.

14. (a) Hodgkins, J. E.; Reeves, W. P., *J. Org. Chem.* **1964**, *29*, 3098. (b) Itoh, K.; Lee, I. K.; Matsuda, I.; Sakai, S.; Ishii, Y., *Tetrahedron Lett.* **1967**, 2667.
15. Sakai, S.; Aizawa, T.; Fujinami, T., *J. Org. Chem.* **1974**, *39*, 1970.
16. (a) Van Alphen, J., *Recl. Trav. Chim. Pays-Bas* **1940**, *59*, 31. (b) Zienty, F. B., *J. Am. Chem. Soc.* **1946**, *68*, 1388. (c) Donia, R. A.; Shotton, J. A.; Bentz, L. O.; Smith, G. E. P., Jr., *J. Org. Chem.* **1949**, *14*, 946. (d) Schröder, D. C., *Chem. Rev.* **1955**, *55*, 181. (e) Davies, S. G.; Mortlock, A. A., *Tetrahedron* **1993**, *49*, 4419.
17. (a) Van Allan, J. A.; Deacon, B. D., *Org. Synth.* **1950**, *30*, 56. (b) Balsiger, R. W.; Fikes, A. L.; Johnston, T. P.; Montgomery, J. A., *J. Org. Chem.* **1961**, *26*, 3386.
18. Katritzky, A. R.; Marson, C. M.; Faid-Allah, H., *Heterocycles* **1987**, *26*, 1657.
19. (a) Carrington, H. C., *J. Chem. Soc* **1948**, 1619. (b) Schulze, W.; Letsch, H.; Willitzen, H., *J. Prakt. Chem.* **1963**, *19*, 101.
20. Batty, J. W.; Weedon, B. C. L., *J. Chem. Soc.* **1949**, 786.
21. Ahlbrecht, H.; Kornetzky, D., *Synthesis* **1988**, 775.
22. (a) Corey, E. J., *Pure Appl. Chem.* **1967**, *14*, 19. (b) Seebach, D., *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
23. (a) Savignac, P.; Dreux, M.; Leroux, Y., *Tetrahedron Lett.* **1974**, 2651. (b) Seebach, D.; Enders, D., *Chem. Ber.* **1975**, *108*, 1293. (c) Seebach, D.; Enders, D., *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15. (d) Seebach, D.; Enders, D.; Renger, B., *Chem. Ber.* **1977**, *110*, 1852. (e) Hassel, T.; Seebach, D., *Helv. Chim. Acta* **1978**, *61*, 2237. (f) Schlecker, R.; Seebach, D., *Helv. Chim. Acta* **1978**, *61*, 512. (g) Lubosch, W.; Seebach, D., *Helv. Chim. Acta* **1980**, *63*, 102. (h) Seebach, D.; Yoshifuji, M., *Helv. Chim. Acta* **1981**, *64*, 643. (i) Beak, P.; Zajdel, W. J., *J. Am. Chem. Soc.* **1984**, *106*, 1010. (j) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L., *J. Org. Chem.* **1986**, *51*, 3076. (k) Meyers, A. I.; Dickman, D. A., *J. Am. Chem. Soc.* **1987**, *109*, 1263. (l) Gawley, R. E., *J. Am. Chem. Soc.* **1987**, *109*, 1265. (m) Gonzales, M. A.; Meyers, A. I., *Tetrahedron Lett.* **1989**, *30*, 43.
24. (a) Mayer, R.; Gewald, K., *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 246. (b) Mayer, R.; Laban, G.; Wirth, M., *Justus Liebigs Ann. Chem./Liebigs Ann. Chem.* **1967**, *703*, 140.
25. Gompper, R.; Wetzel, B.; Elser, W., *Tetrahedron Lett.* **1968**, 5519.
26. (a) Gompper, R.; Schaefer, H., *Chem. Ber.* **1967**, *100*, 591. (b) Shahak, I.; Sasson, Y., *Tetrahedron Lett.* **1973**, 4207. (c) Fukada, N.; Arai, K.; Takeshima, T., *Synthesis* **1980**, 566. (d) Dieter, R. K., *J. Org. Chem.* **1981**, *46*, 5031. (e) Apparao, S.; Ila, H.; Junjappa, H., *Synthesis* **1981**, 65. (f) Villemin, D.; Alloum, A. B., *Synthesis* **1991**, 301.
27. Corey, E. J.; Chen, R. H. K., *Tetrahedron Lett.* **1973**, 3817.
28. Fujinami, T.; Wakuda, K.; Takahashi, N.; Sakai, S., *Chem. Lett.* **1982**, 123.
29. Clausen, R. P.; Becker, J., *Tetrahedron* **1996**, *52*, 3171.
30. Takimiya, K.; Morikami, A.; Otsubo, T., *Synlett* **1997**, 319.
31. Kodani, M.; Murakami, S.; Jigami, T.; Takimiya, K.; Aso, Y.; Otsubo, T., *Heterocycles* **2001**, *54*, 225.
32. Takimiya, K.; Jigami, T.; Kawashima, M.; Kodani, M.; Aso, Y.; Otsubo, T., *J. Org. Chem.* **2002**, *67*, 4218.
33. Rufino, A. R.; Biaggio, F. C., *Tetrahedron Lett.* **2001**, *42*, 8559.
34. Casar, Z.; Leban, I.; Maréchal M.-L.; Lorcy, D., *J. Chem. Soc., Perkin Trans. 1* **2002**, 1568.
35. Liu, Y.; Chen, X.; Xue, M.; Cao, R.; Liu, L., *Synthesis* **2003**, 195.
36. Marchand, P.; Gulea, M.; Masson, S.; Saquet, M.; Collignon, N., *Org. Lett.* **2000**, *2*, 3757.
37. Alberti, A.; Benaglia, M.; Laus, M.; Sparnacci, K., *J. Org. Chem.* **2002**, *67*, 7911.
38. Fox, D. L.; Whitely, N. R.; Cohen, R. J.; Salvatore, R. N., *Synlett* **2003**, 2037.
39. Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K., *J. Am. Chem. Soc.* **2005**, *127*, 605.
40. Tanaka, K.; Wada, A.; Noguchi, K., *Org. Lett.* **2006**, *8*, 907.

Cerium(IV) Ammonium Sulfate[1]

$Ce(NH_4)_4(SO_4)_4 \cdot 2H_2O$

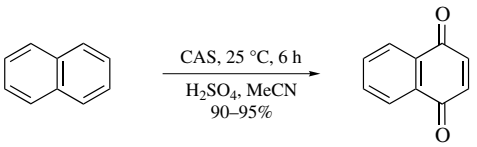
($\cdot 2H_2O$)
[7637-03-8] $CeH_{16}N_4O_{16}S_4$ (MW 596.52)
InChI = 1/Ce.4H3N.4H2O4S/c;;;;;4*1-5(2,3)4/h;4*1H3;4*(H2,1,2,3,4)/q+4;;;;;;;;/p-4/fCe.4H4N.4O4S/h;4*1H;;;;/qm;4*+1;4*-2
InChIKey = OKJMLYFJRFYBPS-PMNQXKOTCT
[10378-47-9] $H_{20}CeN_4O_{18}S_4$ (MW 632.55)
InChI = 1/Ce.4H3N.4H2O4S.2H2O/c;;;;;4*1-5(2,3)4;;/h;4*1H3;4*(H2,1,2,3,4);2*1H2/q+4;;;;;;;;;;/p-4/fCe.4H4N.4O4S.2H2O/h;4*1H;;;;;;/qm;4*+1;4*-2;;
InChIKey = VCNAMBGKEDPVGQ-LFZNXPSQCB

(convenient reagent for oxidation of aromatic rings,[2] and halophenols to quinones,[6] for regioselective Baeyer–Villiger oxidation,[11] and oxidative aromatization[12])

Alternate Name: ceric ammonium sulfate; CAS.
Physical Data: mp 140 °C (dec).
Solubility: sol water, dil. H_2SO_4, dil. H_2SO_4–MeCN.
Form Supplied in: orange solid, widely available.
Handling, Storage, and Precautions: cerium(IV) ammonium sulfate is a stable reagent and precautions required for handling strong oxidizing agents such as potassium permanganate will be sufficient. Cerium is reputed to be of low toxicity.

Cerium(IV) ion is a potent one-electron oxidant.[1] cerium(IV) ammonium nitrate (CAN), is the most widely utilized cerium(IV) oxidizing agent, but cerium(IV) ammonium sulfate (CAS) is a good substitute when complications due to the involvement of nitrate ligands occur, resulting in side products such as nitrate esters.[1]

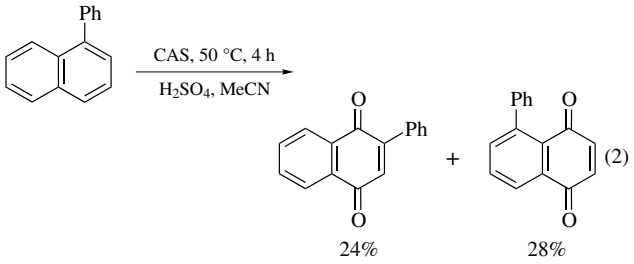
Synthesis of Quinones by Oxidation of Aromatic Rings. The most important application of CAS is in the oxidation of aromatic rings. CAN oxidizes polycyclic aromatic hydrocarbons only in moderate yields (20–60%),[1] and these reactions are often complicated by the formation of nitrate esters.[2] In contrast, CAS generally oxidizes aromatic hydrocarbons to quinones in good yields. For example, naphthalene is oxidized to 1,4-naphthoquinone in excellent yield by CAS in a dilute mixture of H_2SO_4 and MeCN (eq 1).[3]



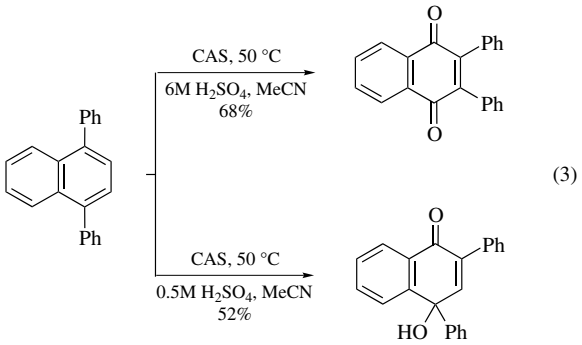
(1)

Other polycyclic aromatic hydrocarbons such as phenanthrene, anthracene, and fluoranthene are converted to the corresponding quinones on oxidation with CAS. Whereas 1-methylnaphthalene gives 1-naphthaldehyde under the conditions,[3] 1-phenyl- and 1-bromonaphthalene react to form some 2-substituted naphthoquinones through an interesting rearrangement (eq 2).[4]

Oxidation of 1,4-diphenylnaphthalene gives 2,3-diphenyl-1,4-naphthoquinone or 4-hydroxy-2,4-diphenyl-1(4*H*)-naphthalenone, depending upon the reaction conditions (eq 3).[5]



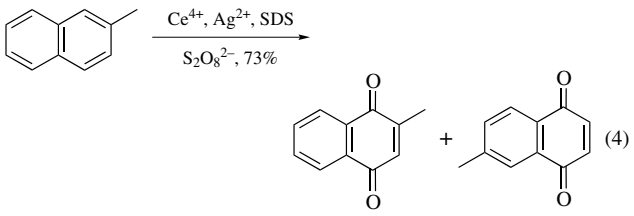
(2)



(3)

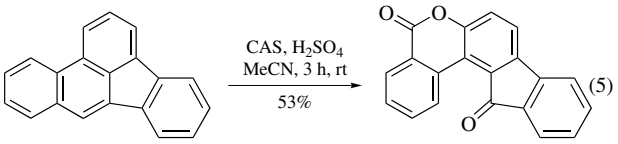
A process utilizing catalytic amounts of Ce^{IV} and Ag^{II} has also been reported (eq 4).[6]

Unfortunately, this reagent system is not suitable for the oxidation of substrates of higher ionization potential nor for oxygen-substituted compounds.



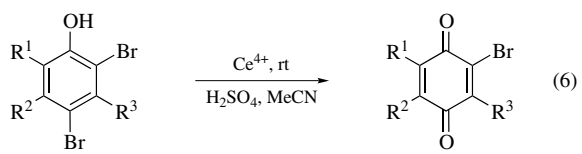
(4)

The major product isolated from the reaction of CAS with benzo[*b*]fluoranthene is a lactone (eq 5).[7]



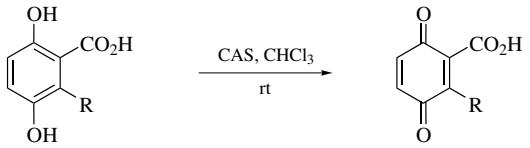
(5)

Oxidation of Phenols to Quinones. Halophenols are conveniently oxidized by CAS to haloquinones in good yields (eq 6).[8] On oxidation with CAS, halonaphthols furnish 1,2-diones as minor products in addition to 1,4-quinones.



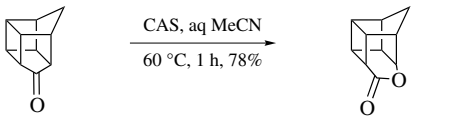
(6)

A direct and convenient route for the conversion of gentisic acid to the corresponding quinone has been developed through the use of CAS in $CHCl_3$ (10% within 15 min) (eq 7).[9]



(7)

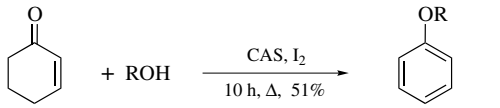
Baeyer–Villiger Oxidation. Oxidation of 1,3-bishomocubanone with a slurry of CAS gives rise to the corresponding lactone (eq 8),[10] which is obtained only as a minor product in the peroxy acid Baeyer–Villiger oxidation conditions.



(8)

Oxidative Halogenation. The reaction of RPh (R = H, Cl, Br, I, Me) with potassium iodide in CF_3CO_2H containing CAS gives a mixture of 2- and 4-RC_6H_4I. Oxidation of methyl 4-methylbenzoate with CAS under the reaction conditions gives exclusively methyl 3-iodo-4-methylbenzoate.[11]

Oxidative Aromatization. A new type of oxidative aromatization of cyclohexenone with the CAS–iodine system has been developed (eq 9).[12]



(9)

1. (a) Ho, T. L. *Synthesis* **1973**, 347. (b) Beletskaya, I. P.; Makhankov, D. I. *Russ. Chem. Rev. (Engl. Transl.)* **1981**, *50*, 534.
2. Rindone, B.; Scolastico, C. *J. Chem. Soc. (B)* **1971**, 2238.
3. Periasamy, M.; Bhatt, M. V. *Synthesis* **1977**, 330.
4. Periasamy, M.; Bhatt, M. V. *Tetrahedron Lett.* **1977**, 2357.
5. Bhatt, M. V.; Periasamy, M. *Tetrahedron* **1994**, *50*, 3575.
6. Sharzewski, J. *Tetrahedron* **1984**, *40*, 4997.
7. Balanikas, G.; Hussain, N.; Amin, S.; Hecht, S. S. *J. Org. Chem.* **1988**, *53*, 1007.
8. Gopinathan, M. B.; Bhatt, M. V. *Indian J. Chem., Sect. B* **1981**, *20B*, 71.
9. Holmes, Jr., J. T.; Vennerstorm, J. J.; Choi, K. E. *J. Org. Chem.* **1984**, *49*, 4736.
10. Mehta, G.; Pandey, P. N.; Ho, T. L. *J. Org. Chem.* **1976**, *41*, 953.
11. Makhonkov, D. I.; Cheprakov, A. V.; Rodkin, M. A.; Beletskaya, I. P.; *Zh. Org. Khim.* **1986**, *22*, 1117 (*Chem. Abstr.* **1988**, *108*, 5616p).
12. Horiuchi, C. A.; Fukunishi, H.; Kajita, M.; Yamaguchi, A.; Kiyomiya, H.; Kiji, S. *Chem. Lett.* **1991**, 1921.

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Cesium Fluoroxysulfate

$CsOSO_2OF$

[70806-67-6] $CsFO_4S$ (MW 247.96)

InChI = 1/Cs.FHO4S/c;1-5-6(2,3)4/h;(H,2,3,4)/q+1;/p-1/fCs.FO4S/qm;-1

InChIKey = ISLBSUZRYCRXSH-NHJKUMIXCQ

(mild fluorinating agent capable of electrophilic addition to C=C bonds[1–3] and fluorofunctionalization of saturated hydrocarbons,[4,5] aromatics,[6–10] ketones and β-diketones,[11,12] enol acetates,[2–12] organosilicon[11] and organotin[13,14] derivatives, etc.)

Solubility: insol cold water; gives 0.07 M soln in acetonitrile.

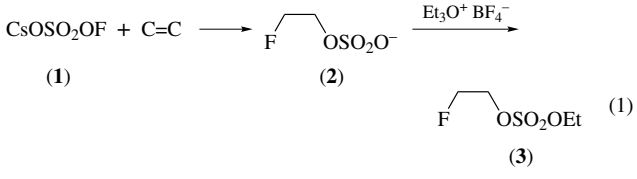
Analysis of Reagent Purity: iodometric titration.[15]

Preparative Method: the reagent can be readily prepared from dilute fluorine and Cs_2SO_4: fluorine (20% mixture with nitrogen) was passed into Cs_2SO_4 in a polyethylene vessel with cooling to −4 °C. The yellowish-white precipitate is centrifuged, washed with a little water, and dried in vacuo.[8,15]

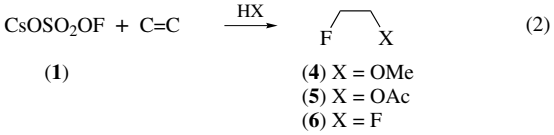
Handling, Storage, and Precautions: the synthesis of up to 200 g of $CsOSO_2OF$ has been described.[8] The reagent is easily handled, provided due care is taken not to cause detonation: avoid mechanical pressure (sharp strikes), any contact with a metallic spatula,[15] and do not heat. A protective shield should always be used. The reagent has been stored in a polyethylene vessel at 0 °C for 14 days without significant loss of activity.[8]

Fluorination. The main result of $CsOSO_2OF$ reactions with various organic substrates is electrophilic fluorination, the hypofluorite moiety in the anionic fragment $FOSO_2O^-$ serving as the F^+ synthon.

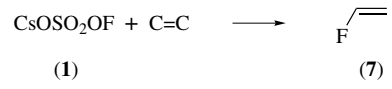
Unsaturated compounds react readily with $CsOSO_2OF$ (**1**) to yield products of addition, of addition with incorporation of solvent or external nucleophile, and of addition–elimination, depending on the reaction conditions. The reactions of (**1**) with alkenes gives 1,2-addition products (**2**), which can be conveniently transformed into ethyl sulfates (**3**) by treatment with $Et_3O^+BF_4^-$ (eq 1).[1] The same reaction in the presence of methanol (rt, CH_2Cl_2) gives β-methoxyalkyl fluorides (**4**). Analogously, reactions in AcOH and HF give vicinal fluoroacetates (**5**) and difluorides (**6**), respectively (eq 2).[2,3] In some cases the reaction proceeds to give vinyl fluorides (**7**) (eq 3). For example, interaction of 1,1-diphenylethylene with (**1**) gives 2-fluoro-1,1-diphenylethylene.[2] Fluorination of norbornene gives a 1:1 mixture of 2-fluoronortricyclene and 7-*syn*-fluoronorbornene.[2]



(1)



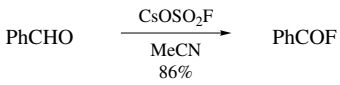
(2)



(3)

Reaction of the reagent (**1**) with 1,2-diphenylacetylene in methanol gives a mixture of 1,1-difluoro-2,2-dimethoxy-1,2-diphenylethane and 2,2-difluoro-1,2-diphenylethanone.[16]

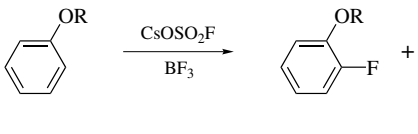
Aromatic and aliphatic aldehydes react with $CsOSO_2OF$, giving acid fluorides in good yields, presumably via radical pathways (eq 4).[4]



(4)

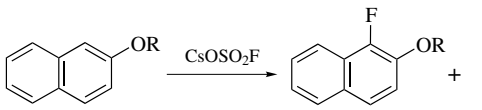
Room temperature fluorination of cyclic enol acetates by (**1**) gives α-fluorocycloalkanones in high yield (70–90%).[2] β-Diketones and barbituric acid give the corresponding *gem*-difluorinated derivatives.[11,12] Room temperature fluorination of uridine in methanol followed by treatment with Et_3N gives 5-fluorouridine (79%).[11] Similarly, 1,3-dimethyluracil gives the 5-fluoro derivative (89%).[11]

Cesium fluoroxysulfate is a mild fluorinating agent for activated aromatics,[6–10] such as phenols (eq 5), alkoxy-substituted benzenes, and naphthalenes. The reaction is catalyzed by HF, H_2SO_4, CF_3SO_3H, FSO_3H,[6] and BF_3.[9]



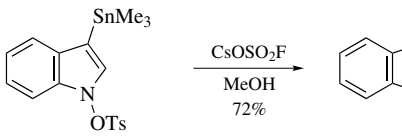
(5)

The reaction of toluene with $CsOSO_2OF$ in acetonitrile gives benzyl fluoride as the principal product,[7] but in the presence of catalysts, *o*- and *p*-fluorotoluenes (6:1) are produced.[6] In some cases of aromatic substitution the formation of fluorinated cyclohexadienones is observed (eq 6).[9]



(6)

Trimethylchlorosilane reacts smoothly with $CsOSO_2OF$ to give trimethylfluorosilane.[11] Trimethyltin-substituted alkenes give fluoroalkenes (eq 7).[13]



(7)

Oxidation. The reagent (**1**) easily oxidizes secondary alcohols to ketones, and 1,2-dihydroxy-4-butylbenzene to the quinone derivative.[17] Ph_3P and dibenzothiophene are oxidized in room temperature reactions with $CsOSO_2OF$.[5,11]

Related Reagents. Chlorine Fluoroxysulfate; (2-Chloro-1,1,2-trifluoroethyl)diethylamine; Fluorine; *N*-Fluoro-*N*-*t*-butyl-*p*-toluenesulfonamide; Dibromomethane.

1. Zefirov, N. S.; Zhdankin, V. V.; Koz'min, A. S.; Fainzilberg, A. A.; Gakh, A. A.; Ugrak, B. I.; Romaniko, S. V., *Tetrahedron* **1988**, *44*, 6505.
2. Stavber, S.; Zupan, M., *J. Chem. Soc., Chem. Commun.* **1981**, 795.
3. Stavber, S.; Zupan, M., *J. Org. Chem.* **1987**, *52*, 919.
4. Stavber, S.; Planinšek, Z.; Zupan, M., *J. Org. Chem.* **1992**, *57*, 5334.
5. Stavber, S.; Zupan, M., *Tetrahedron* **1989**, *45*, 2737.
6. Appleman, E. H.; Basile, L. J.; Hayatsu, R. *Tetrahedron* **1984**, *40*, 189.
7. Ip, D. P.; Arthur, C. D.; Winans, R. E.; Appleman, E. H., *J. Am. Chem. Soc.* **1981**, *103*, 1964.
8. Stavber, S.; Zupan, M., *J. Org. Chem.* **1985**, *50*, 3609.
9. Stavber, S.; Zupan, M., *J. Chem. Soc., Chem. Commun.* **1981**, 148.
10. Stavber, S.; Zupan, M., *J. Fluorine Chem.* **1981**, *17*, 597.
11. Stavber, S.; Zupan, M., *J. Chem. Soc., Chem. Commun.* **1983**, 563.
12. Stavber, S.; Šket, B.; Zajc, B.; Zupan, M., *Tetrahedron* **1989**, *45*, 6003.
13. Hodson, H. F.; Madge, D. J.; Widdowson, D. A., *Synlett* **1992**, 831.
14. Bryce, M. R.; Chambers, R. D.; Mullins, S. T.; Parkin, A., *J. Chem. Soc., Chem. Commun.* **1986**, 1623.
15. Appleman, E. H.; Basile, L. J.; Thompson, R. C., *J. Am. Chem. Soc.* **1979**, *101*, 3384.
16. Stavber, S.; Zupan, M., *J. Org. Chem.* **1987**, *52*, 5022.
17. Stavber, S.; Zupan, M., *Tetrahedron* **1992**, *48*, 5875.

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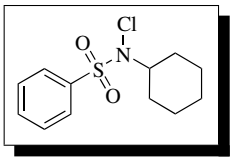
N-Chloro-*N*-cyclohexylbenzenesulfonamide[1]



[15963-66-3] $C_{12}H_{16}ClNO_2S$ (MW 273.78)
InChI = 1/C12H16ClNO2S/c13-14(11-7-3-1-4-8-11)17(15,16)12-9-5-2-6-10-12/h2,5-6,9-11H,1,3-4,7-8H2
InChIKey = RWVOAAWFMJRINI-UHFFFAOYAT

(used for radical chlorination at allylic[1,4] or benzylic carbon[1])

Physical Data: mp 42 °C.

Solubility: sol benzene, CCl_4, $CHCl_3$, CH_2Cl_2; insol H_2O, petroleum ether.

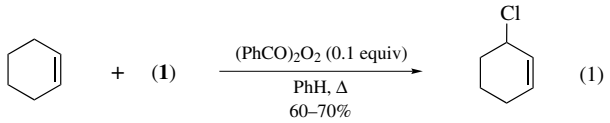
Analysis of Reagent Purity: mp, NMR, combustion analysis.

Preparative Methods: N-cyclohexylbenzenesulfonamide can be prepared by addition of benzenesulfonyl chloride to a solution of cyclohexylamine in pyridine and purified by recrystallization from ethanol. *N*-Chlorination is accomplished by treating a solution of *N*-cyclohexylbenzenesulfonamide in dichloromethane with NaOCl solution at 0 °C followed by dropwise addition of glacial acetic acid.[1] Alternatively, a suspension of *N*-cyclohexylbenzenesulfonamide in acetic acid can be treated with NaOCl solution or powdered *N*-cyclohexylbenzenesulfonamide can be added to a solution containing $NaHCO_3$ and NaOCl.[2]

Purification: precipitation from $CHCl_3$ solution by addition of petroleum ether or trituration with petroleum ether.

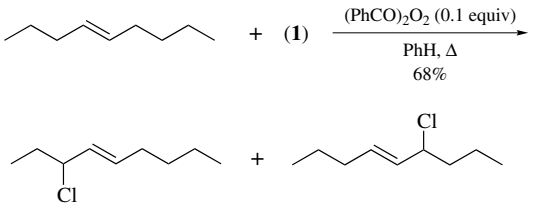
Handling, Storage, and Precautions: to avoid decomposition, this reagent should be protected from prolonged exposure to light and moisture. Store under nitrogen in the dark. This toxic reagent should be handled in a fume hood.

Allylic Chlorination. This reagent (**1**) has been used as a chlorine source in radical chlorination of allylic and benzylic positions. Treatment of alkenes bearing allylic carbon–hydrogen bonds with (**1**) in refluxing benzene in the presence of a radical initiator such as dibenzoyl peroxide results in the formation of allyl chlorides in good to moderate yields (eq 1).[1]

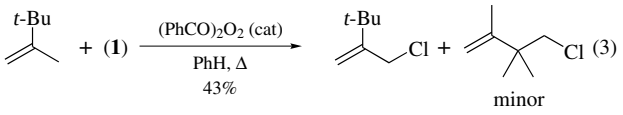


(1)

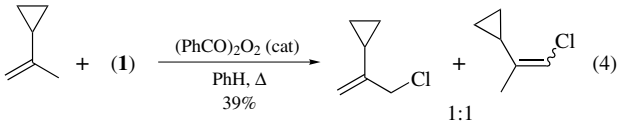
As with the more commonly used chlorinating agent *N*-chlorosuccinimide, this chlorination proceeds via a radical chain reaction in which Cl_2 is liberated and reacts with a carbon radical.[3] Consequently, isomeric mixtures are often obtained (eqs 2–4).[1,4]



(2)



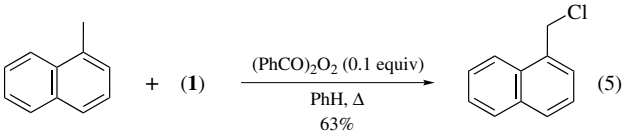
(3)



(4)

Separation of the resulting isomeric products is often difficult. For example, the isomeric chlorinated products in eq 4 were separated from one another using preparative gas chromatography.[4] *N*-Cyclohexylbenzenesulfonamide precipitates upon cooling of the reaction mixture and can be recovered by filtration.[1]

Chlorination at benzylic positions proceeds in good yields (eq 5).[1]



(5)

Related Reagents. *t*-Butyl Hypochlorite; *N*-Chlorosuccinimide; Hypochlorous Acid; Phenylselenium Trichloride.

1. Theilacker, W.; Wessel, H., *Justus Liebigs Ann. Chem.* **1967**, *703*, 34.
2. Yuki, H.; Kishikawa, T.; Tohira, Y.; Suzuki, S.; Sano, F.; Hayakawa, S., *Chem. Pharm. Bull.* **1967**, *15*, 1123.
3. Dauben, H. J.; McCoy, L. L., *J. Am. Chem. Soc.* **1959**, *81*, 4863.
4. Cristol, S. J.; Daughenbaugh, R. J., *J. Org. Chem.* **1979**, *44*, 3434.

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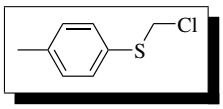
Chloromethyl *p*-Tolyl Sulfide[1]



[34125-84-3] C_8H_9ClS (MW 172.68)
InChI = 1/C8H9ClS/c1-7-2-4-8(5-3-7)10-6-9/h2-5H,6H2,1H3
InChIKey = VFQYMJYUSRAJCZ-UHFFFAOYAX

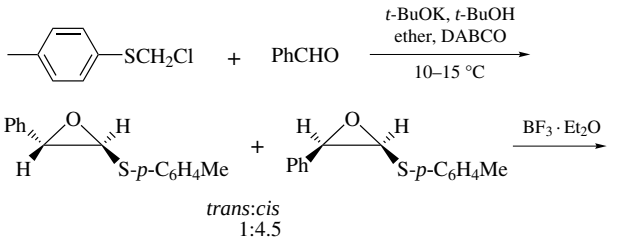
(source of the *p*-tolylthio carbanion[2] and reactive electrophiles;[1] starting material for the synthesis of 1-halomethyl *p*-tolyl sulfoxide[3])

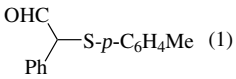
Physical Data: bp 125–126 °C/15 mmHg.
Solubility: sol most organic solvents; insol H_2O.
Preparative Methods: several methods are available.[4] The most commonly used and convenient method is the chlorination of methyl *p*-tolyl sulfide with sulfuryl chloride in methylene chloride.[4a,b]
Handling, Storage, and Precaution: use in a fume hood.

Chloromethyl *p*-Tolyl Sulfide Carbanion. The reaction of *p*-tolylthiochloromethylpotassium, generated by the reaction of chloromethyl *p*-tolyl sulfide with potassium tert-butoxide in *t*-butanol in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), with benzaldehyde gives the corresponding α,β-epoxy sulfide as a mixture of isomers, the *cis* isomer being the predominant product. When pivalaldehyde is used as the carbonyl component, only the *cis* isomer of the corresponding α,β-epoxy sulfide is formed. The *cis* isomers upon treatment with boron trifluoride etherate rearrange to α-tolylthio aldehydes with the exclusive migration of the *p*-tolylthio group (eq 1).[2a] This type of rearrangement is analogous to the reaction of α,β-epoxy sulfoxides[5].

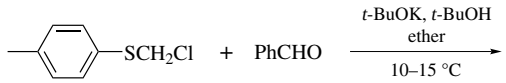
Attempts to generate *p*-tolylthiochloromethylpotassium with *t*-butoxide in *t*-butanol without DABCO in the presence of the carbonyl compounds gave only *trans*-1,2-bis(*p*-tolylthio)ethylene as a byproduct, presumably by a displacement–elimination reaction involving the *p*-tolylthiochloromethyl carbanion (eq 2).[2a]

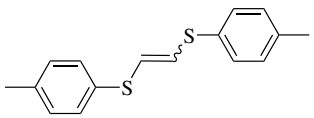
A low yield of β-hydroxy-α-chloro sulfide is obtained from the reaction of *p*-tolylthiochloromethyllithium with benzaldehyde, presumably due to the inefficient generation of the carbanion with *n*-butyllithium. The phenylthio analog of the α,β-epoxy sulfide is prepared by the reaction of bis(phenylthio)methyllithium with carbonyl compounds. The adducts, α-hydroxybis(phenylthio) acetals, on reaction with copper(I) trifluoromethanesulfonate (6 equiv) in benzene containing diisopropylethylamine (4 equiv), give α,β-epoxy sulfides which are thermally labile and undergo thermal rearrangement to α-phenylthio ketones (eq 3).[6]



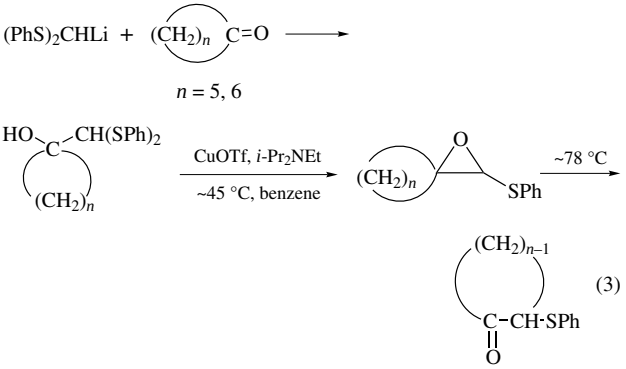


(1)



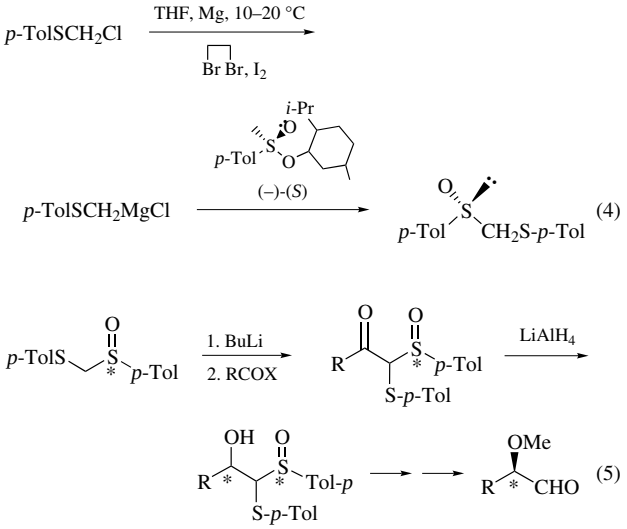


(2)

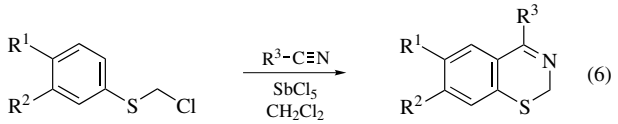


(3)

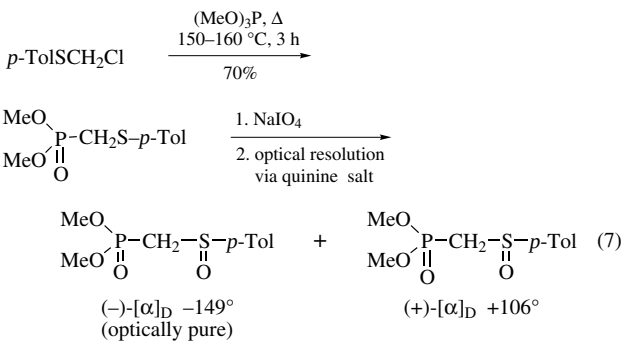
A high yield of a Grignard reagent, *p*-tolylthiomethylmagnesium chloride, is obtained by the reaction of chloromethyl *p*-tolyl sulfide with magnesium in THF at 10–20 °C. The temperature is the crucial factor, and small amounts of iodine and 1,2-dibromoethane are used to initiate the Grignard reaction. (+)-(*S*)-*p*-Tolyl *p*-tolylthiomethyl sulfoxide is formed in 81% yield with 88% optical purity upon reacting an equimolar amount of the Grignard reagent with (−)-(*S*)-menthyl *p*-toluenesulfinate (eq 4).[2b] This method is used for preparation of the chiral thioacetal monosulfoxide with a higher chemical yield but lower optical purity than the method reported earlier, which utilizes *p*-tolylthiomethyllithium as the carbanion partner.[7] The chiral thioacetal monosulfoxide is useful as a chiral synthon for the synthesis of chiral α-substituted aldehydes (eq 5).[8]

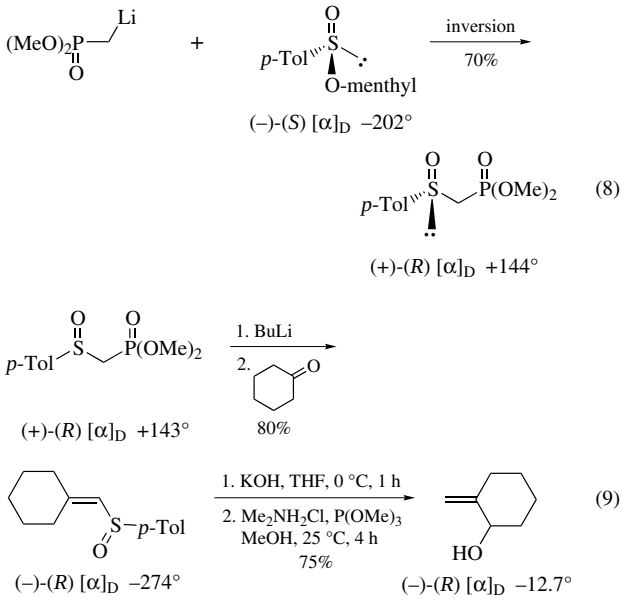


***N*-Alkylation.** 2*H*-1,3-Benzothiazine derivatives, a group of compounds with significant pharmacological activities, are synthesized by *N*-alkylation followed by cyclization of aryl and alkyl nitriles using antimony(V) chloride as a Lewis acid (eq 6).[9]

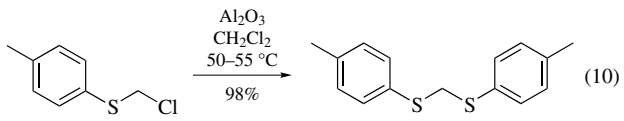


***P*-Alkylation.** The Michael–Arbuzov reaction of chloromethyl *p*-tolyl sulfide with trimethyl Phosphite[10] or triethyl phosphite[11] yields dimethyl- or diethylphosphonylmethyl *p*-tolyl sulfides, which are important intermediates for the synthesis of vinyl sulfides and sulfoxides,[12] as well as for optically active derivatives of dimethylphosphonylmethyl *p*-tolyl sulfoxide (eq 7). This method of preparation of the chiral *p*-tolylthio monosulfoxide is complementary to the reaction using dimethylphosphonylmethyllithium and (−)-(*S*)-menthyl *p*-toluenesulfinate in which the (+)-(*R*) isomer is obtained in high yield and high optical purity (eq 8). The lithio dimethylphosphonylmethyl *p*-tolyl sulfoxide reacts with aldehydes and ketones to give the corresponding vinyl sulfoxides, which can be converted into optically active allylic alcohols (eq 9).[10,13]

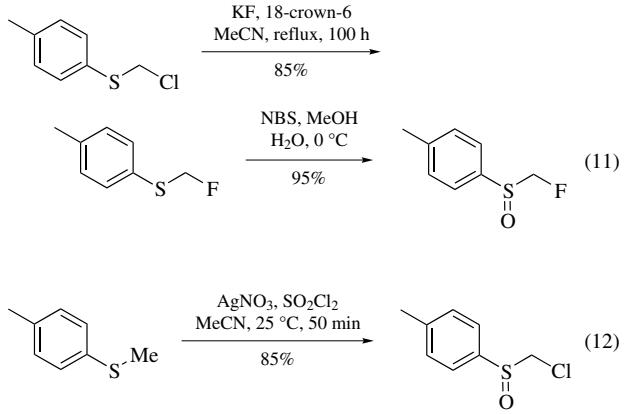




Self-condensation. Bis(*p*-tolylthio)methane, an important dithioacetal for nucleophilic alkylation,[14] is formed by self-alkylation of chloromethyl *p*-tolyl sulfide using neutral alumina as a catalyst (eq 10).[15]



Oxidation. Fluoromethyl *p*-tolyl sulfide, which can be oxidized to fluoromethyl *p*-tolyl sulfoxide with *N*-bromosuccinimide in methanol, is synthesized by the reaction of chloromethyl *p*-tolyl sulfide with potassium fluoride in the presence of 18-crown-6 (eq 11).[3b] Chloromethyl *p*-tolyl sulfoxide can be synthesized by a one-pot operation from methyl *p*-tolyl sulfide with silver(I) nitrate and sulfuryl chloride via the intermediacy of chloromethyl *p*-tolyl sulfide (eq 12).[3b,c]



1. (a) Dilworth, B. M.; McKervey, M. A., *Tetrahedron* **1986**, *42*, 3731. (b) Barrett, G. C. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ed.; Pergamon: Oxford, 1979; Vol. 3, Chapter 11.4. (c) Nudelman, A.

The Chemistry of Optically Active Sulfur Compounds; Gordon & Breach: New York, 1984.

2. (a) Tavares, D. F.; Estep, R. E., *Tetrahedron Lett.* **1973**, 1229. (b) Ogura, K.; Fujita, M.; Takahashi, M.; Takahashi, K.; Iida, H., *Tetrahedron Lett.* **1982**, 1679.
3. (a) Hojo, M.; Masuda, R., *Tetrahedron Lett.* **1976**, 613. (b) More, K. M.; Wemple, J., *Synthesis* **1977**, 791. (c) Kim, Y. H.; Shin, H. H.; Park, Y. J., *Synthesis* **1993**, 209.
4. (a) Bordwell, F. G.; Cooper, G. D.; Morita, H., *J. Am. Chem. Soc.* **1957**, *79*, 376. (b) Trost, B. M.; Kunz, R. A., *J. Org. Chem.* **1974**, *39*, 2648. (c) Goralski, C. T.; Burk, G. A., *J. Org. Chem.* **1977**, *42*, 3094. (d) Ono, N.; Miyake, H.; Saito, T.; Kaji, A., *Synthesis* **1980**, 952.
5. (a) Tavares, D. F.; Estep, R. E.; Blezard, M., *Tetrahedron Lett.* **1970**, 2373. (b) Durst, T.; Tin, K.-C., *Tetrahedron Lett.* **1970**, 2369.
6. Cohen, T.; Kuhn, D.; Falck, J. R., *J. Am. Chem. Soc.* **1975**, *97*, 4749.
7. Colombo, L.; Gennari, C.; Narisano, E., *Tetrahedron Lett.* **1978**, 3861.
8. Guanti, G.; Narisano, E.; Banfi, L.; Scolastico, C., *Tetrahedron Lett.* **1983**, *24*, 817.
9. Thakur, D. K.; Vankar, Y. D., *Synthesis* **1983**, 223.
10. Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczynska, A., *J. Org. Chem.* **1978**, *43*, 473.
11. Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T., *Synth. Commun.* **1986**, *16*, 233.
12. (a) Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A., *Synthesis* **1975**, 278. (b) Mikolajczyk, M.; Grzejsczak, S.; Midura, W.; Zatorski, A., *Synthesis* **1976**, 396.
13. Hoffman, R. W.; Maak, N., *Tetrahedron Lett.* **1976**, 2237.
14. Gröbel, B.-T.; Seebach, D., *Synthesis* **1977**, 357.
15. (a) Campbell, M. M.; Jigajinni, V. B.; MacLean, K. A.; Wightman, R. H., *Tetrahedron Lett.* **1980**, *21*, 3305. (b) Jigajinni, V. B.; Wightman, R. H., *J. Chem. Soc., Chem. Commun.* **1981**, 87.

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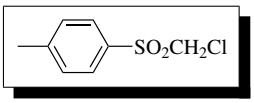
Chloromethyl *p*-Tolyl Sulfone

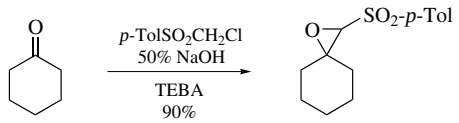


[7569-26-8] $C_8H_9ClO_2S$ (MW 204.68)
InChI = 1/C8H9ClO2S/c1-7-2-4-8(5-3-7)12(10,11)6-9/h2-5H, 6H2,1H3
InChIKey = ZQPJNJKCPJDTIQ-UHFFFAOYAK

(synthesis of α,β-epoxy sulfones and alkylated sulfones;[1] reacts with electrophilic arenes and heterocyclic arenes;[2] source of α-*p*-tolylsulfonyl radicals[1a])

Physical Data: mp 81–82 °C.
Solubility: sol THF, $CHCl_3$, CH_2Cl_2, and most organic solvents.
Preparative Methods: by oxidation of the corresponding sulfoxide[3] or by reaction of sodium *p*-toluenesulfinate with bromochloromethane.[4]
Handling, Storage, and Precaution: use in a fume hood.

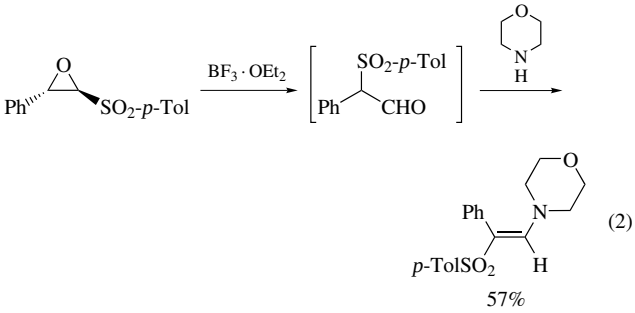
α,β-Epoxy Sulfones. The chemistry of chloromethyl *p*-tolyl sulfone resembles that of chloromethyl phenyl sulfone α,β-Epoxy *p*-tolyl sulfones derived from carbonyl compounds are conveniently prepared by a one-step Darzens-type condensation using benzyltriethylammonium chloride (TEBA) as phase-transfer catalyst, and 50% sodium hydroxide as a base (eq 1).[4a,5] *trans*-α,β-Epoxy *p*-tolyl sulfones, and a mixture of *cis* and *trans* isomers, are obtained from aldehydes and unsymmetrical ketones, respectively.



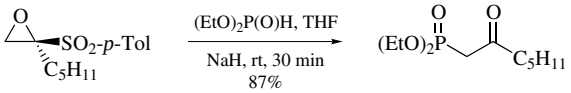
(1)

α,β-Epoxy *p*-tolyl sulfones can also be prepared by the epoxidation of α,β-unsaturated *p*-tolyl sulfones with alkaline hydrogen peroxide (giving *trans*-α,β-epoxy *p*-tolyl sulfones)[6] and potassium chlorite (producing *cis*-α,β-epoxy *p*-tolyl sulfones).[7]

α,β-Epoxy *p*-tolyl sulfones undergo reactions similar to those of α,β-epoxy phenyl sulfones. Rearrangement with boron trifluoride etherate gives the expected α-tolylsulfonyl substituted carbonyl products (eq 2).[5b] The reaction with sodium diethyl phosphite gives synthetically useful α-keto phosphonates (eq 3).[8]

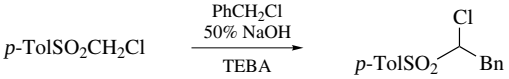


(2)

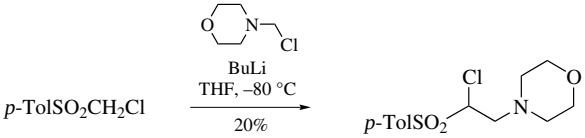


(3)

Alkylation Reactions. Alkylation of chloromethyl *p*-tolyl sulfone with alkyl halides can be effected either by using a phase-transfer catalyst or butyllithium as a base (eqs 4 and 5).[5a,9] *p*-Tolylsulfonylchloromethylmagnesium, prepared by the reaction with ethylmagnesium bromide, is stable and undergoes normal Grignard reactions, e.g., carbonylation and carbonyl addition reactions.[10]



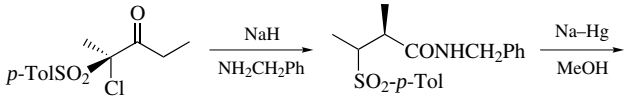
(4)



(5)

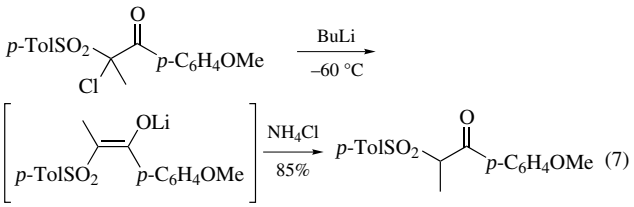
Reaction of α-Alkylated Sulfones. Racemic and optically active α-chloro-β-keto *p*-tolyl sulfones, prepared by oxidation of the corresponding sulfoxides, undergo Favorskii rearrangement

to give α-alkyl amides. This process can be used to synthesize optically active α-alkyl amides by the asymmetric Favorskii rearrangement (eq 6).[11] α-Chloro-α-alkyl-β-keto *p*-tolyl sulfones undergo metal–halogen exchange with *n*-butyllithium to give the corresponding enolates which can be protonated to give substituted α-*p*-tolylsulfonyl derivatives (eq 7).[12]



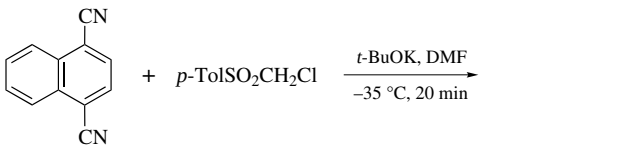
(6)

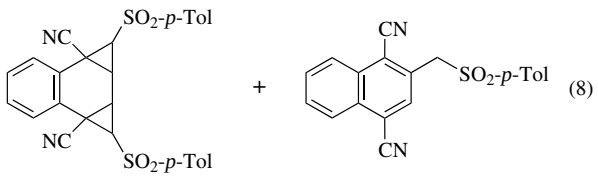
$[\alpha]_D$ –14.36°, 85% ee



(7)

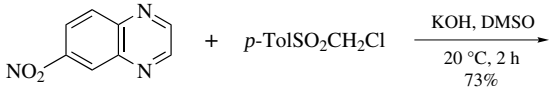
Vicarious Nucleophilic Aromatic Substitution of Hydrogen (VNS). The chloromethyl *p*-tolyl sulfone carbanion behaves similarly to the corresponding phenyl analog in the vicarious nucleophilic substitution of hydrogen (VNS) with electrophilic arenes and heterocyclic arenes.[2] The reaction with 1,4-dicyanonaphthalene gives both the VNS product and the corresponding bis(cyclopropane) derivative (eq 8).[13] The reaction with 6-nitroquinoxaline gives the normal VNS product (eq 9),[13] whereas the reaction with 6-azaquinoxaline gives either VNS and/or the corresponding bis(cyclopropane) products depending on temperature, the base used and its concentration (eq 10).[14]

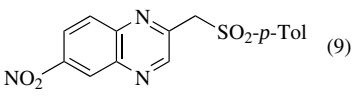




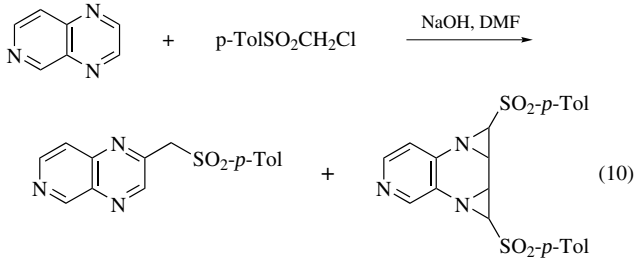
(8)

33% 26%





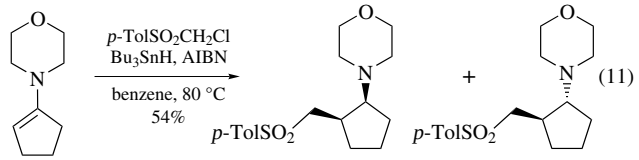
(9)



(10)

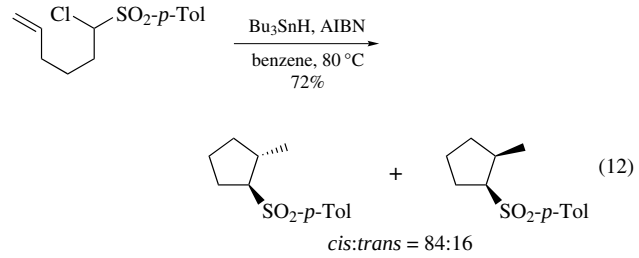
20 °C	0%	84%
–10 °C	25%	23%
–30 °C	44%	0%

Radical Reactions. The α-*p*-tolylsulfonylmethyl radical, generated using either tributyltin hydride, azobisisobutyronitrile,[15] or hexabutyldistannane with UV irradiation,[16] adds to enol ethers, enamines, and silyl enol ethers. The addition to enamines shows considerable *syn* diastereoselectivity which can be explained on the basis of an allylic 1,3-strain model (eq 11). When an alkenic or alkynic moiety is present in the α-substituent of the α-*p*-tolylsulfonylmethyl radical, cyclization can occur to give five-membered ring compounds (eqs 12 and 13).[15b,17]



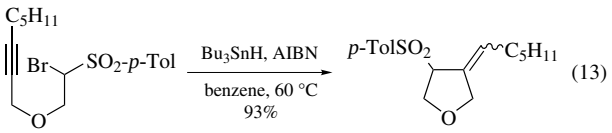
(11)

cis:*trans* = 84:16



(12)

cis:*trans* = 84:16



(13)

1. (a) Magnus, P. D., *Tetrahedron* **1977**, *33*, 2019. (b) Durst, T. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ed.; Pergamon: Oxford, 1979; Vol. 3, p 171. (c) Krief, A., *Comprehensive Organic Synthesis* **1991**, *3*, 85. (d) Simpkins, N. S., *Sulfones in Organic Synthesis*; Pergamon: Oxford, 1993.
2. (a) Makosza, M.; Winiarski, J., *Acc. Chem. Res.* **1987**, *20*, 282. (b) Makosza, M., *Synthesis* **1991**, 103.
3. Cinquini, M.; Colonna, S., *J. Chem. Soc., Perkin Trans. 1* **1972**, 1883.
4. Vogt, P. F.; Tavares, D. F., *Synlett* **1969**, *47*, 2875.
5. (a) Jończyk, A.; Bańko, K.; Makosza, M., *J. Org. Chem.* **1975**, *40*, 266. (b) Houwen-Claassen, A. A. M.; McFarland, J. W.; Lammerink, B. H. M.; Thijs, J.; Zwanenburg, B., *Synthesis* **1983**, 628.
6. Zwanenburg, B.; Wiel, J. T., *Tetrahedron Lett.* **1970**, 935.
7. Curci, R.; DiFuria, F., *Tetrahedron Lett.* **1974**, 4085.

8. Koh, Y. J.; Oh, D. Y., *Tetrahedron Lett.* **1993**, *34*, 2147.
9. Böhme, H.; Stammberger, W., *Justus Liebigs Ann. Chem.* **1971**, *754*, 56.
10. Stetter, H.; Steinbeck, K., *Justus Liebigs Ann. Chem.* **1972**, *766*, 89.
11. (a) Satoh, T.; Oguro, K.; Shishikura, J.; Kanetaka, N.; Okada, R.; Yamakawa, K., *Tetrahedron Lett.* **1992**, *33*, 1455. (b) Satoh, T.; Motohashi, S.; Kimura, S.; Tokutake, N.; Yamakawa, K., *Tetrahedron Lett.* **1993**, *34*, 4823. (c) Satoh, T.; Oguro, K.; Shishikura, J.; Kanetaka, N.; Okada, R.; Yamakawa, K., *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2339.
12. Satoh, T.; Shishikura, J.; Hayashi, Y.; Yamakawa, K., *Chem. Lett.* **1992**, 381.
13. Makosza, M.; Glinka, T.; Ostrowski, S.; Rykowski, A., *Chem. Lett.* **1987**, 61.
14. Ostrowski, S.; Makosza, M., *Tetrahedron* **1988**, *44*, 1721.
15. (a) Renaud, P., *Tetrahedron Lett.* **1990**, *31*, 4601. (b) Renaud, P.; Schubert, S., *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 433. (c) Schubert, S.; Renaud, P.; Carrupt, P.-A.; Schenk, K., *Helv. Chim. Acta* **1993**, *76*, 2473.
16. Harendza, M.; Junggebauer, J.; Lessmann, K.; Neumann, W. P.; Tews, H., *Synlett* **1993**, 286.
17. Ueno, Y.; Khare, R. K.; Okawara, M., *J. Chem. Soc., Perkin Trans. 1* **1983**, 2637.

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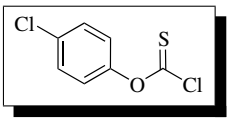
4-Chlorophenyl Chlorothionoformate

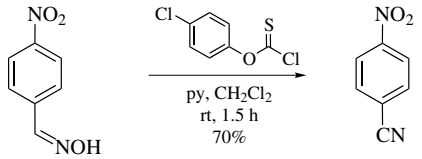


[937-64-4] $C_7H_4Cl_2OS$ (MW 207.08)
InChI = 1/C7H4Cl2OS/c8-5-1-3-6(4-2-5)10-7(9)11/h1-4H
InChIKey = BQIABQCJXBELMT-UHFFFAOYAO

(dehydrating agent;[1] has been used in radical deoxygenation;[2] serves as a building block in the synthesis of penems[3] and heterocycles;[4] used for introduction of the thiocarbonyl group[5])

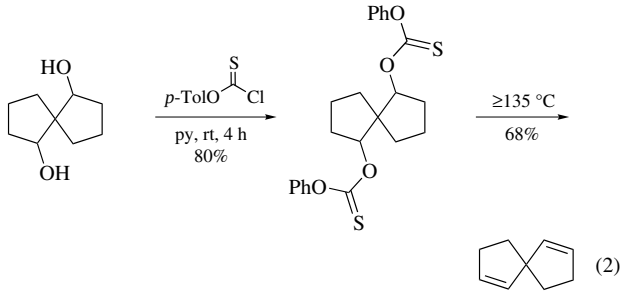
Alternate Name: O-(4-chlorophenyl) carbonochloridothioate.
Physical Data: bp 82 °C/0.8 mmHg;[6] 114–116 °C/0.8 mmHg.[7]
Form Supplied in: distillable liquid; commercially available.
Preparative Method: from thiophosgene and *p*-chlorophenol in the presence of sodium hydroxide.[2,6]
Handling, Storage, and Precaution: protect from moisture.

Use as Dehydrating Agent. The reagent converts oximes to nitriles under mild conditions (rt, 1.5 h) (eq 1).[1]



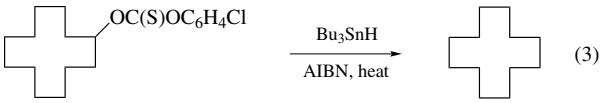
(1)

Use in the Chugaev Reaction. The closely related reagent, *p*-tolyl chlorothionoformate, has been used for Chugaev eliminations (eq 2);[8] presumably, *p*-chlorophenyl chlorothionoformate could serve the same function.



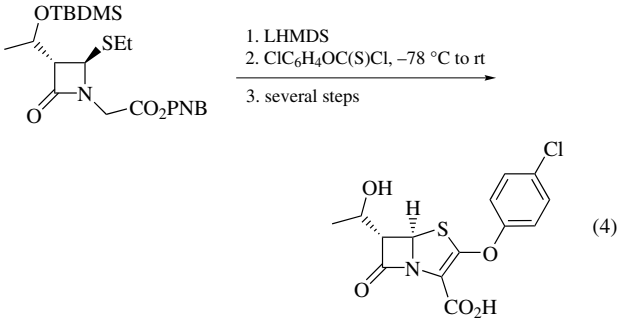
(2)

Use in Radical Deoxygenation. The reagent has been used in radical deoxygenation (eq 3).[2]



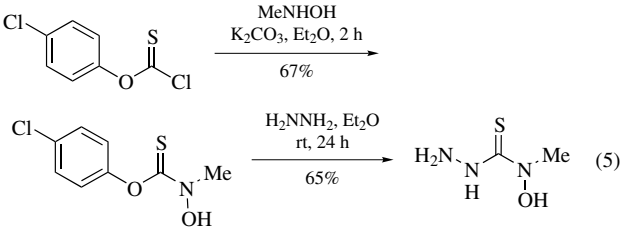
(3)

Use as a Building Block. The reagent has been incorporated into the structure of a thiopenem antibiotic (eq 4).[3]



(4)

The reagent is also useful for introducing the thiocarbonyl function, since the chlorine atom and chlorophenol residues can be replaced successively by nucleophiles (eq 5).[4,5]



(5)

1. Clive, D. L. J., *J. Chem. Soc., Chem. Commun.* **1970**, 1014.
2. Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. Cs., *Tetrahedron* **1992**, *48*, 7435.
3. Cooke, M. D.; Moore, K. W.; Ross, B. C.; Turner, S. E., *J. Chem. Soc., Chem. Commun.* **1983**, 1005.
4. Müller, E.; Gröbner, P., *Monatsh. Chem.* **1975**, *106*, 27.
5. Richter, P.; Oertel, D.; Oertel, F., *Pharmazie* **1988**, *43*, 753 (*Chem. Abstr.* **1989**, *110*, 173 200h).
6. Garmaise, D. L.; Uchiyama, A.; McKay, A. F., *J. Org. Chem.* **1962**, *27*, 4509.
7. Lancaster catalog, 1991/1992.

8. Gerlach, H.; Huong, T. T.; Müller, W., *J. Chem. Soc., Chem. Commun.* **1972**, 1215. Gerlach, H.; Müller, W., *Helv. Chim. Acta* **1972**, *55*, 2277.

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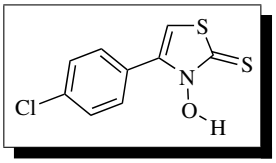
4-(4-Chlorophenyl)-3-hydroxy-2(3*H*)-thiazolethione



[105922-93-8] $C_9H_6NOClS_2$ (MW 243.72)
InChI = 1/C9H6ClNOS2/c10-7-3-1-6(2-4-7)8-5-14-9(13)11(8)12/h1-5,12H
InChIKey = VIRCDYKDYNGPSJ-UHFFFAOYAO

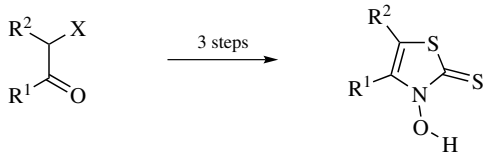
(starting material for the synthesis of *N*-alkoxy-4-(*p*-chlorophenyl) thiazole-2(3*H*) thiones[1,2]—compounds that liberate alkoxyl radicals under neutral (i.e., non-oxidative) conditions, if subjected to microwave irradiation, heated in the presence of an initiator, or photolyzed with either intense visible or UV/A light.[1,3,4] *N*-Alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones exhibit significantly improved characteristics as sources of oxygen-centered radicals for synthetic purposes[4–6] or for the investigation of mechanistic aspects of *O*-radical chemistry,[7] if compared to equivalent reagents such as *N*-alkoxypyridine-2(1*H*)-thiones,[8,9] *N*-alkoxyphthalimides,[10] or *N*-alkoxydithiocarbamates;[11] reagent for the generation of the hydroxyl radical, e.g., for photobiological applications;[12] starting material for the synthesis of *N*-acyloxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thiones[1,13] which serve as carbon radical precursors)

Alternate Names: *N*-hydroxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione, CPTTOH.

Physical Data: decomposes at 138 ± 2 °C in an exothermic reaction without melting; UV/Vis (EtOH): λ_{max} (log ϵ) = 309 (4.16), 240 nm (4.20); ^{1}H, ^{13}C NMR data; FT-IR, single crystal X-ray crystallography; and electronic spectrum have been investigated.[1,14]

Solubility: soluble in many organic solvents (dimethylsulfoxide, dimethylformamide, ethyl acetate, chloroform, dichloromethane, benzene); slightly soluble in THF, methyl *tert*-butyl ether, diethyl ether, and EtOH; almost insoluble in water.

Preparative Methods: CPTTOH and a number of closely related derivatives thereof, such as 4-(*p*-methoxyphenyl)-,4-(*p*-methylphenyl)-, 4-phenyl-, and 4-(*p*-nitrophenyl)-substituted *N*-hydroxythiazole-2(3*H*) thione, *N*-hydroxy-4-methylthiazole-2(3*H*) thione (commercially available), and *N*-hydroxy-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*) thione are prepared from the corresponding α-haloketones in three synthetic steps.[15–17] The yields for the most important reagents of this type are in the range 59–68% (eq 1). Polymer-supported derivatives of CPTTOH have been immobilized on a Wang resin.[18]



(1)

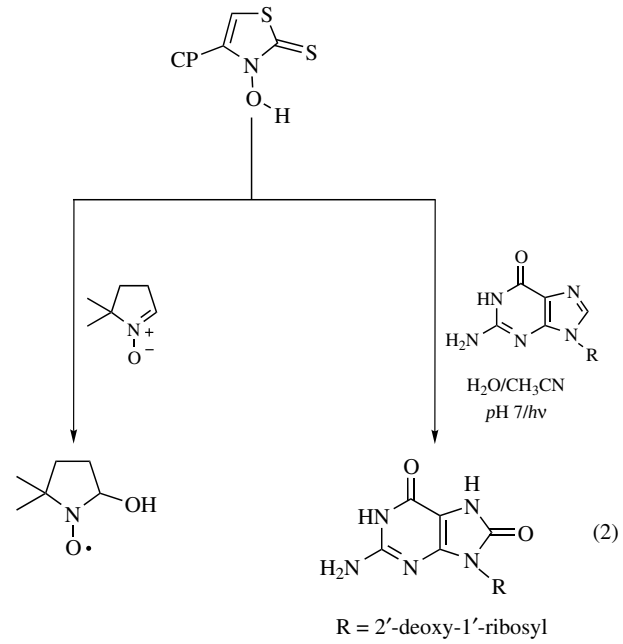
R^1	R^2	X	Yield (%)
p-ClC_6H_4 (CP)	H	Br	67
CH_3	H	Cl	59
CH_3	*p*-$H_3COC_6H_4$ (An)	Cl	68

Handling, Storage, and Precautions: colorless crystalline material (bulk); faces of single crystals shimmer, depending on their orientation towards light, from green to brown. Purification of CPTTOH is achieved by recrystallization of the crude product from hot 2-propanol. The title compound has a musty odor. Inhalation of CPTTOH dust and contact with eyes should be avoided; wearing of protective gloves while handling CPTTOH in a well-ventilated hood and storage in amber-colored vials at temperatures below 20 °C is recommended.

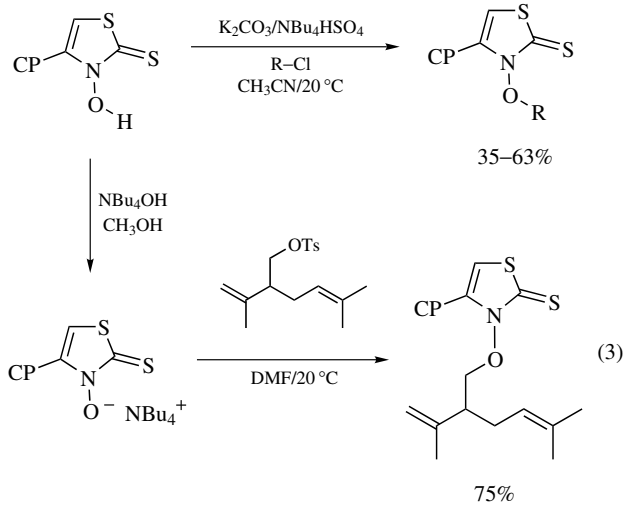
***N*-Hydroxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) Thione.** The reagent is a weak acid which forms monovalent anions if treated with alcoholic solutions of alkaline hydroxides or tetraalkylammonium hydroxides. The derived NEt_4-salts (hygroscopic) are commonly used for the preparation of *N*-alkoxy-4-(*p*-chlorophenyl) thiazole-2(3*H*) thiones.[1,4] Syntheses and X-ray crystallography of bis[*N*-oxy-4-methylthiazole-2-thiolato(–1)]copper(II) and zinc(II) from *N*-hydroxy-4-methylthiazole-2(3*H*) thione have been reported.[19] CPTTOH is an efficient source of the hydroxyl radical under neutral conditions when photolyzed in aq CH_3CN.[12] The hydroxyl radical has been trapped under these conditions with DMPO and identified via the characteristic EPR spectrum of its derived nitroxyl radical adduct (eq 2). Photolysis of CPTTOH in the presence of 2′-deoxyguanosine affords 8-oxo-2′-deoxyguanosine in up to 6% yield (eq 2). Further, the reagent induces strand breaks in supercoiled pBR322 DNA via intermediate photogenerated hydroxyl radicals.[12] In a more recent application, the transformation of CPTTOH and cyclodecyne has been reported to furnish products of transannular cyclization, presumably via addition of a photochemically generated HO • radical to the triple bond in one of the initial steps.[20]

***N*-Alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) Thiones (CPTTOR).** Selective *O*-alkylation of CPTTOH is achieved by treatment of derived NBu_4- or NEt_4-salts[2,4] with hard alkylating reagents such as primary or secondary alkyl chlorides, bromides, tosylates, and brosylates as well as allylic or benzylic chlorides (eq 3). 2-Alkylsulfanyl-4-(*p*-chlorophenyl)thiazole-*N*-oxides, i.e., compounds of *S*-selective alkylation of the ambident thiohydroxamate anion, are formed in minor amounts (<5–10%). The only exception is seen when CPTTOH is treated with an excess of CH_3I thus leading to 2-methylsulfanyl-4-(*p*-chlorophenyl)-thiazole-*N*-oxide as major product.[21,22] The synthesis of chiral *N*-alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones from

secondary alkyl tosylates and *N*-hydroxy-4-(*p*-chlorophenyl) thiazole-2(3*H*) thione tetraalkylammonium salts proceeds under S_N2-conditions. The enantiomeric purity of chiral *N*-alkoxythiazole-2(3*H*) thiones is preferentially verified by CD-spectroscopy. A direct application of CPTTOH in the synthesis of *N*-alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones, which circumvents a separate synthesis of hygroscopic NBu_4- and NEt_4-salts, has been developed. The latter procedure applies K_2CO_3 as base, NBu_4HSO_4 as phase transfer catalyst, CH_3CN as solvent, and preferentially alkyl chlorides or tosylates as alkylating reagents (eq 3).[2] The synthesis of *N*-(1-pentyloxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione (47%) has been achieved starting from 1-pentanol, CPTTOH, DIAD,



(2)



(3)

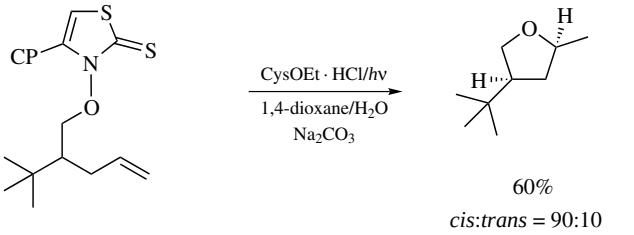
PPh_3 in CH_2Cl_2.[23] The latter procedure has, however, been more effectively adapted for the synthesis of *N*-alkoxy-4-methylthiazole-2(3*H*) thiones using DEAD as azo compound and C_6H_6 as solvent.[24]

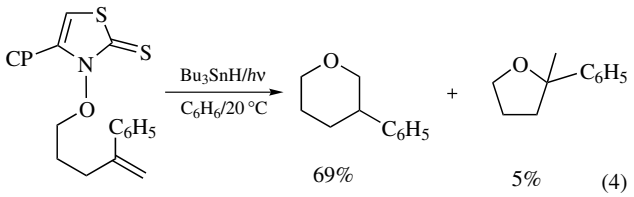
N-Alkoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones are colorless to tan crystalline compounds which may generally be stored for years in a refrigerator. Selected *N*-alkenoxy-4-(*p*-chlorophenyl) thiazole-2(3*H*) thiones have been heated in C_6H_6 ($T = 80$ °C) for 2 h in the presence of α-tocopherol without significant decomposition. Rare examples of thermal transformations of CPTTOR, which proceed at ~5 °C in the dark, refer to fragmentations or isomerizations of selected neat samples. Thus, *N*-(5-methyl-1-phenyl-4-hexenoxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione fragments upon longer storage into 5-methyl-1-phenyl-4-hexen-1-one and 4-(*p*-chlorophenyl)thiazole-2(3*H*) thione. *N*-Methoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione rearranges into 2-methylsulfanyl-4-(*p*-chlorophenyl)thiazole, and *N*-(3-*tert*-butyl-4-penten-1-oxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione isomerizes into 2-[*cis*-(4-*tert*-butyltetrahydrofuryl-2-methylsulfanyl)]-4-(*p*-chlorophenyl)thiazole.[21] A rare instance of thiazolethione ring cleavage, which afforded among other products a derived isothiocyanate, has been observed in photochemical experiments starting from *N*-isopropoxy-4-(*p*-methylphenyl)thiazole-2(3*H*) thione.[25] Photochemical excitation (250 W, visible light discharge lamp or Rayonet®-chamber reactor equipped with 350 nm light bulbs), treatment with BEt_3/O_2, or heating of solutions of CPTTOR in the presence of an initiator (e.g., AIBN) affords alkoxyl radicals RO• that have been applied in efficient chain reactions for selective C–O bond formations (synthesis of cyclic ethers), β-C-C cleavages (formation of aldehydes), and remote functionalizations. Efficient transformations of all three types require the use of appropriate mediators that furnish after carbon radical trapping suitable chain carrying radicals. In this sense, $\bullet CCl_3$ (from, e.g., $BrCCl_3$), *n*-$\bullet C_4F_9$ (from *n*-C_4F_9I), $\bullet SnBu_3$ (from $HSnBu_3$), and $\bullet Si(SiMe_3)_3$ [from $HSi(SiMe_3)_3$] are favorable intermediates because they readily add to the C=S π-bond in *N*-alkoxythiazole-2(3*H*) thiones thus inducing selective N-O-homolysis and therefore alkoxyl radical generation. Primary and secondary alkyl radicals are generally not suited for this purpose.[7]

Carbon–Oxygen Bond Formation. Photolysis of δ-unsaturated *N*-alkenoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones in the presence of trapping reagents leads to the formation of substituted tetrahydrofurans and/or tetrahydropyrans. The key step of this reaction is associated with an intramolecular C–O bond formation of intermediate substituted 4-penten-1-oxyl radicals. Cyclized radicals are preferentially trapped with L-cysteine derivatives (in aqueous solvents) or Bu_3SnH, $(Me_3Si)_3SiH$ (in organic solvents) (eq 4). 1- or 3-Substituted 4-penten-1-oxyl radicals afford 2,5-*trans*- or 2,3-*trans*-disubstituted tetrahydrofurans as major products. The observed diastereoselectivity increases with the steric size in the series Me < Et < *i*-Pr < *t*-Bu < 2,4,6-mesityl for 1-substituted radicals. Cyclizations of 2-substituted 4-penten-1-oxyl radicals provide 2,4-*cis*-disubstituted tetrahydrofurans. The *cis*-selectivity improves in going from Me via Ph to *t*-Bu.[26] A minor fraction of 6-*endo* cyclized products (i.e., substituted tetrahydropyrans) is formed in most cases. The ratio of 5-*exo*:6-*endo* cyclized products is determined by the substituent at position 4 of the 4-penten-1-oxyl radical and increases in the sequence 4-Me < 4-*t*-Bu < 4-Ph from 82:18 to 7:93 at 30 °C.

For synthetic purposes, cyclized radicals are preferentially trapped with halogen atom donors such as CCl_4, $BrCCl_3$,

n-C_4F_9I, I(Me)C(CO_2Et)$_2$.[4,9] The latter reaction, which constitutes a radical version of the halocyclization, is a synthetically useful transformation. It is the only known method so far for selectively converting 5,5-dimethyl-substituted bis-homoallylic alcohols, a widespread structural motif among naturally occurring terpenols, into 5-*exo*-halocyclized products without notable interference of tetrahydropyran formation (eq 5).[4,5] In other instances, complementary diastereoselectivities of alkoxyl radical based bromocyclizations have been observed, if compared to the polar equivalent starting from bis-homoallylic alcohols and, e.g., NBS. For example, photolysis of (2*R*,3*S*)-*N*-(3-benzoyloxy-5-hexen-2-oxy)-4-methylthiazole-2(3*H*) thione in the presence of $BrCCl_3$ furnishes (2*R*,3*S*,5*S*)-3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofuran as the major product and the corresponding (2*R*,3*S*,5*R*)-isomer as the minor. These building blocks were converted into enantiomerically pure (+)-*allo*-muscarine (from the major alkoxyl radical cyclization product) and (–)-muscarine (from the minor product) (eq 6). The polar bromocyclization of (2*R*,3*S*)-3-benzoyloxy-5-hexen-2-ol exhibits a reversed diastereoselectivity thus leading to (2*R*,3*S*,5*R*)-3-benzoyloxy-5-bromomethyl-2-methyltetrahydrofuran, i.e., the precursor of (−)-muscarine, as major product.[27,28]





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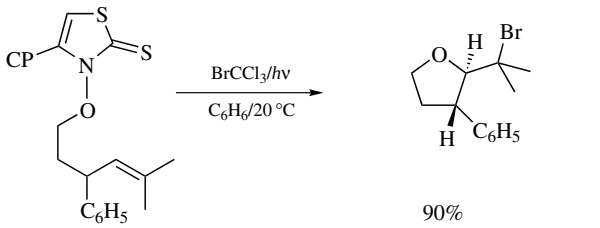
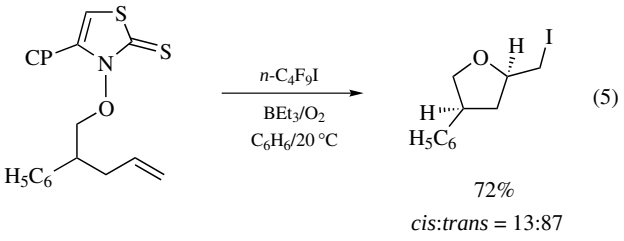
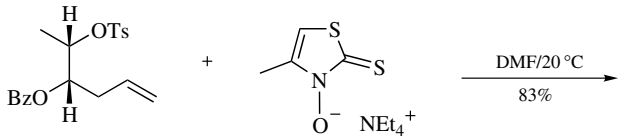
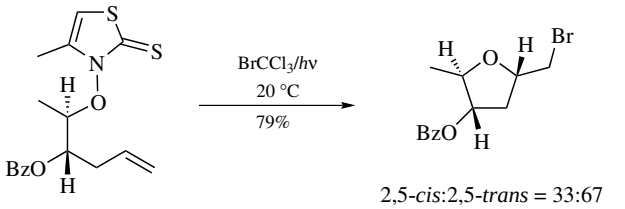


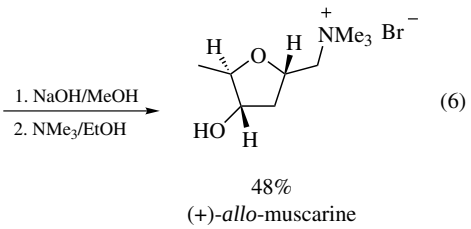


(5)

***β*-Carbon–Carbon Bond Cleavage.** Thermal or photochemical excitation of strained *N*-(cycloalkoxy)thiazole-2(3*H*) thiones, preferentially in the presence of Bu_3SnH or $(Me_3Si)_3SiH$, leads to the formation of synthetically useful aldehydes or ketones (eq 7). Acetal-derived oxyl radicals generally provide the corresponding substituted formates as crude products which are frequently converted in the course of the chromatographic work-up into the derived alcohols (eq 7).[7,17,24] Most of such transformations have been performed either with 4-methyl- or with 5-(*p*-methoxyphenyl)-4-methyl-substituted thiazole-2(3*H*) thiones. This is due to (i) improved yields for the synthesis of such alkoxyl radical precursors and (ii) favorable characteristics especially of 5-(*p*-methoxyphenyl)-4-methyl-substituted thiazolethiones.[17] The alkoxyl radical-induced C–C cleavage is particularly useful for degrading carbohydrate-derived hydroxyl groups with subsequent heteroatom trapping or C–C-bond formation.[29,30]







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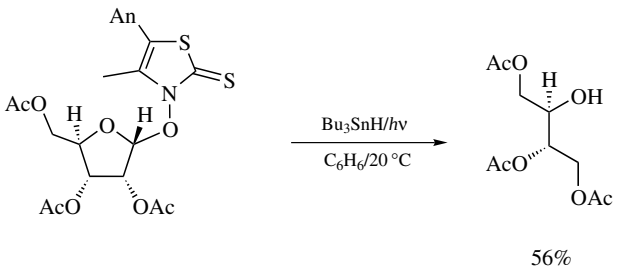
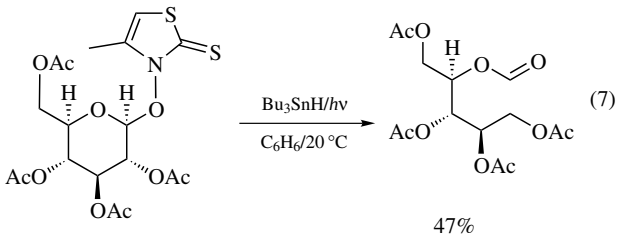
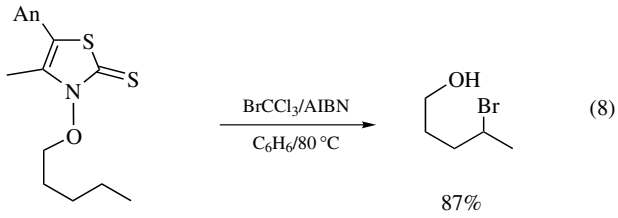




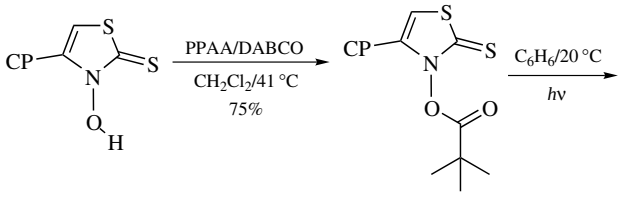
(7)

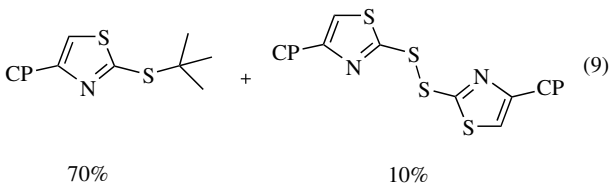
Remote Functionalization: C–H Activation. Substituted *N*-(alkoxy)thiazolethiones have been applied in selective C–H activation reactions. For example, δ-bromohydrins that serve as starting materials for succeeding polar transformations have been prepared from *N*-(1-pentyloxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*) thione and $BrCCl_3$ (eq 8). This reaction is preferentially conducted under thermal conditions since the effectiveness of the underlying 1,5-hydrogen translocation benefits from elevated temperatures.[17]



(8)

***N*-Acyloxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) Thiones [CPTTOC(O)Rs].** Treatment of *N*-hydroxy-4-(*p*-chlorophenyl) thiazole-2(3*H*) thione potassium salt with acyl chlorides or alkyl chloroformates furnishes CPTTOC(O)Rs.[4,20] Polymer-supported derivatives of CPTTOH have been transformed via intermediate salt formation into the corresponding *N*-acyloxy derivatives.[18] A direct conversion of carboxylic acids, for instance pivaloic acid, and CPTTOH into the derived *N*-acyloxy-4-(*p*-chlorophenyl)thiazole-2(3*H*) thiones is feasible if propane trisphosphonic acid anhydride (PPAA) is used as dehydrating reagent.[13,31] *N*-(Pivaloyloxy)-4-(*p*-chlorophenyl)thiazole-2(3*H*) thione, or solid-phase supported derivatives thereof, liberate upon heating or photochemical excitation *tert*-butyl radicals that have been trapped with, e.g., $BrCCl_3$ to furnish *tert*-butyl bromide.[18] In the absence of a suitable trapping reagent, *N*-(pivaloyloxy)-4-(*p*-chlorophenyl) thiazole-2(3*H*) thione is converted into 2-*tert*-butylsulfanyl-4-(*p*-chlorophenyl)thiazole as major and 2,2′-bis[4-(*p*-chlorophenyl) thiazyl]disulfane as minor product (decarboxylative rearrangement) (eq 9).[1]





70% 10%

(9)

Related Reagents. *N*-Hydroxypyridine-2-thione; 4-Methyl-3-hydroxythiazole-2-thione; 5-(*p*-Methoxyphenyl)-4-methyl-3-hydroxythiazole-2-thione; (Diacetoxyiodo)benzene; *N*-Hydroxyphthalimide.

1. Hartung, J.; Schwarz, M.; Svoboda, I.; Fuess, H.; Duarte, M. T., *Eur. J. Org. Chem.* **1999**, 1275.
2. Hartung, J.; Kneuer, R.; Schwarz, M.; Svoboda, I.; Fuess, H., *Eur. J. Org. Chem.* **1999**, 97.
3. Hartung, J.; Špehar, K., to be published.
4. Hartung, J.; Kneuer, R.; Schmidt, P.; Laug, S.; Špehar, K.; Svoboda, I.; Fuess, H., *Eur. J. Org. Chem.* **2003**, 4033.
5. Hartung, J.; Kneuer, R.; Kopf, T. M.; Schmidt, P., *C. R. Acad. Sci. Paris, Chim.* **2001**, 649.
6. Hartung, J.; Kneuer, R., *Eur. J. Org. Chem.* **2000**, 1677.
7. Hartung, J.; Gottwald, T.; Špehar, K., *Synthesis* **2002**, 1469.
8. Beckwith, A. L. J.; Hay, B. P., *J. Am. Chem. Soc.* **1988**, *110*, 4415.
9. Hartung, J.; Gallou, F., *J. Org. Chem.* **1995**, *60*, 6706.
10. Kim, S.; Lee, T. A.; Song, Y., *Synlett* **1998**, 471.
11. Kim, S.; Lim, C. K.; Song, S.-E.; Kang, H.-Y., *Synlett* **2001**, 688.
12. Adam, W.; Hartung, J.; Okamoto, H.; Saha-Möller, C. R.; Špehar, K., *Photochem. Photobiol.* **2000**, *75*, 619.
13. Hartung, J.; Schwarz, M., *Synlett* **2000**, 371.
14. Engels, B.; Arnone, M.; Špehar, K.; Hartung, J., submitted.
15. Hartung, J.; Schwarz, M., *Org. Synth.* **2002**, *79*, 228.
16. Barton, D. H. R.; Crich, D.; Kretzschmar, G., *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.
17. Hartung, J.; Gottwald, T.; Špehar, K., *Synlett* **2003**, 227.
18. De Luca, L.; Giacomelli, G.; Porcu, G.; Taddei, M., *Org. Lett.* **2001**, *3*, 855.
19. Bond, A. D.; Jones, W., *J. Chem. Soc., Dalton Trans.* **2001**, 3045.
20. Wille, U.; Jargstorff, C., *J. Chem. Soc., Perkin Trans. 1* **2002**, 1036.
21. Hartung, J.; Špehar, K.; Svoboda, I.; Fuess, H., to be published.
22. Walter, W.; Schaumann, E., *Synthesis* **1971**, 111.
23. Hartung, J., *Habilitation Thesis*, Würzburg, 1998.
24. Hartung, J.; Gottwald, T.; Kneuer, R., *Synlett* **2001**, 749.
25. Adam, W.; Hartung, J.; Okamoto, H.; Marquardt, S.; Nau, W. M.; Pischel, U.; Saha-Möller, C. R.; Špehar, K., *J. Org. Chem.* **2002**, *67*, 6041.
26. Hartung, J., *Eur. J. Org. Chem.* **2001**, 619.
27. Hartung, J.; Kneuer, R., *Tetrahedron: Asymmetry* **2003**, *14*, 3019.
28. Hartung, J.; Kunz, P.; Laug, S.; Schmidt, P., *Synlett* **2003**, 51.
29. de Armas, P.; García-Tellado, F.; Marrero-Tellado, J. J.; Robbles, J., *Tetrahedron Lett.* **1997**, *38*, 8081.
30. González, C. C.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E., *Angew. Chem., Int. Ed.* **2001**, *40*, 2326.
31. Wissmann, H.; Kleiner, H. J., *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 134.

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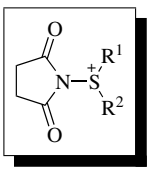
N-Chlorosuccinimide–Dimethyl Sulfide[1]



($R^1 = R^2 = Me$)

[39095-38-0] $C_6H_{10}ClNO_2S$ (MW 195.66)

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InChIKey = AIOGDEPLLOKDKL-WDBQYWFPCZ

(R^1 = Me, R^2 = Et)
[54959-52-3] $C_7H_{12}ClNO_2S$ (MW 209.69)
InChI = 1/C7H12NO2S.ClH/c1-3-11(2)8-6(9)4-5-7(8)10;/h3-5H2,1-2H3;1H/q+1;/p-1/fC7H12NO2S.Cl/h;1h/qm;-1
InChIKey = MRXLPEWZJSYDHY-NWEYTFLYCX
(R^1 = Me, R^2 = *n*-Pr)
[54959-53-4] $C_8H_{14}ClNO_2S$ (MW 223.72)
InChI = 1/C8H14NO2S.ClH/c1-3-6-12(2)9-7(10)4-5-8(9)11;/h3-6H2,1-2H3;1H/q+1;/p-1/fC8H14NO2S.Cl/h;1h/qm;-1
InChIKey = OOQSEVGUAWSAJU-KKPWASROCD
(R^1 = Et, R^2 = $CH_2CH{=}CH_2$)
[59321-40-3] $C_9H_{14}ClNO_2S$ (MW 235.73)
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InChIKey = FHJIQCRGOAFTNR-FBUAAAOSCP
(R^1 = Me, R^2 = CH_2CHMe_2)
[54959-54-5] $C_9H_{16}ClNO_2S$ (MW 237.74)
InChI = 1/C9H16NO2S.ClH/c1-7(2)6-13(3)10-8(11)4-5-9(10)12;/h7H,4-6H2,1-3H3;1H/q+1;/p-1/fC9H16NO2S.Cl/h;1h/qm;-1
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(R^1 = R^2 = *n*-Pr)
[59741-19-4] $C_{10}H_{18}ClNO_2S$ (MW 251.77)
InChI = 1/C10H18NO2S.ClH/c1-3-7-14(8-4-2)11-9(12)5-6-10(11)13;/h3-8H2,1-2H3;1H/q+1;/p-1/fC10H18NO2S.Cl/h;1h/qm;-1
InChIKey = ZHTSQHYYQFKZGF-DEUOUNQNCT
(R^1 = Me, R^2 = Ph)
[82661-92-5] $C_{11}H_{12}ClNO_2S$ (MW 257.73)
InChI = 1/C11H12NO2S.ClH/c1-15(9-5-3-2-4-6-9)12-10(13)7-8-11(12)14;/h2-6H,7-8H2,1H3;1H/q+1;/p-1/fC11H12NO2S.Cl/h;1h/qm;-1
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(R^1 = Et, R^2 = $CH_2CH{=}CMe_2$)
[59321-43-6] $C_{11}H_{18}ClNO_2S$ (MW 263.78)
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InChIKey = YTFNBZBLNRIMTE-SXLUFDMMCV
(R^1 = Me, R^2 = CH_2Ph)
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InChIKey = MALVRSWFEYFPLJ-QXPKJTSLCY
(R^1 = Et, R^2 = CH_2Ph)
[65824-51-3] $C_{13}H_{16}ClNO_2S$ (MW 285.79)
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InChIKey = IRNAMJBJHJHFEX-KISFJZJQCD
(R^1 = Et, R^2 = $CH_2C_6H_4$-4-Me)
[65824-52-4] $C_{14}H_{18}ClNO_2S$ (MW 299.82)
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(R^1 = Et, R^2 = $CH_2(1\text{-}C_{10}H_7)$
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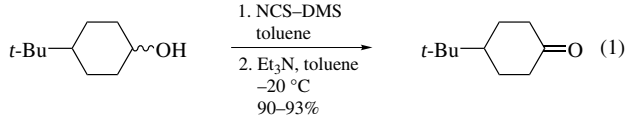
InChIKey = TXRVUQPACKYWEO-QTGCJPJXCX
(R^1 = R^2 = *n*-C_7H_{15})
[59741-21-8] $C_{20}H_{38}ClNO_2S$ (MW 392.04)
InChI = 1/C18H34NO2S.ClH/c1-3-5-7-9-11-15-22(16-12-10-8-6-4-2)19-17(20)13-14-18(19)21;/h3-16H2,1-2H3;1H/q+1;/p-1/fC18H34NO2S.Cl/h;1h/qm;-1
InChIKey = WRJUSNALBIGEAD-HBUBGDDHCB

(oxidizing agent for alcohols to aldehydes and ketones,[1] catechols and hydroquinones to quinones,[2] aromatic amines to sulfilimines,[3] hydroxamic acids to acylnitroso compounds;[4] chlorination of allylic and benzylic alcohols,[5] *ortho* alkylation and formylation of phenols,[6] preparation of chloromethyl thioethers,[7] thioalkylation of pyrroles, indoles, and enamines;[8] preparation of sulfur ylides of active methylene compounds,[9] preparation of sulfonium salts from enamines and cyclopentadienyl anions,[10] dehydration to form keto enamines from β-diketones and nitriles from aldoximes[11])

Alternate Names: Corey–Kim reagent; dimethyl(succinimido)-sulfonuim chloride.
Physical Data: R^1 = R^2 = Me: mp 70–72 °C.
Solubility: the reagents are slightly more sol in CH_2Cl_2, toluene, and THF than the NCS from which they are derived.
Form Supplied in: prepared in situ from NCS and dialkyl sulfides.
Handling, Storage, and Precautions: see *N*-Chlorosuccinimide, dimethyl sulfide, and other articles on alkyl sulfides.

***N*-Chlorosuccinimide–Dialkyl Sulfides.** These reagents are generally prepared in situ in solvents such as toluene, CH_2Cl_2, or THF. The reagents themselves are generally more soluble than the NCS from which they are derived and are often prepared at a temperature of about 0 °C to facilitate reaction with the limitedly soluble NCS, but because of their thermal instability are not prepared at higher temperature. They are often used at temperatures as low as −78 °C.

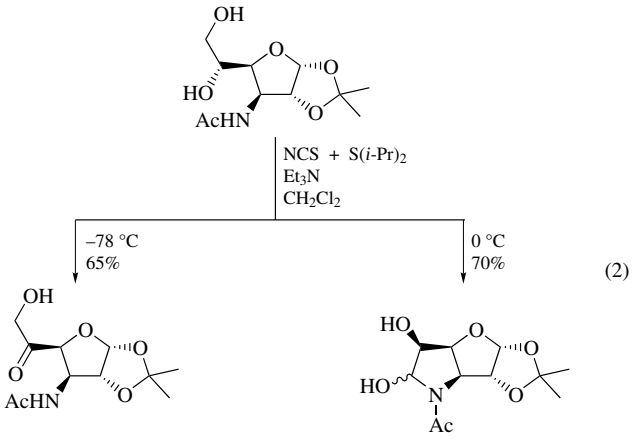
Oxidations. *N*-Chlorosuccinimide–dimethyl sulfide (NCS–DMS) is one of several reagents for converting alcohols to alkoxydimethylsulfonium salts, which in the presence of base convert to the corresponding carbonyl compounds via intramolecular proton transfer and loss of dimethyl sulfoxide.[1,12] These oxidations are among the mildest and most selective for conversions of alcohols to aldehydes and ketones. This reaction does not suffer the overoxidation to acids or the carbon–carbon bond cleavages which are often encountered in chromium(VI) or manganese(VII) oxidations (eq 1).[1,13]



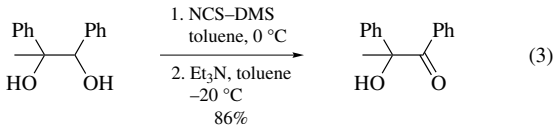
(1)

Several higher members of this class, including the NCS–diisopropyl sulfide reagent, are reported to show unusual selectivity for primary and secondary alcohols. Thus at 0 °C the reagent

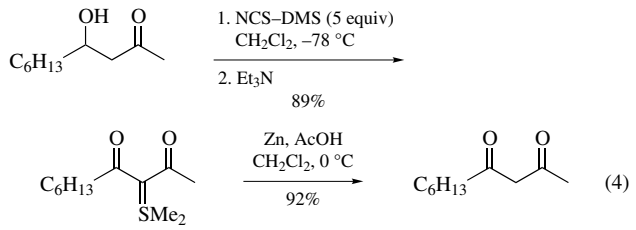
selectively oxidizes primary alcohols rather than secondary, whereas at −78 °C it selectively oxidizes secondary alcohols rather than primary (eq 2).[14]



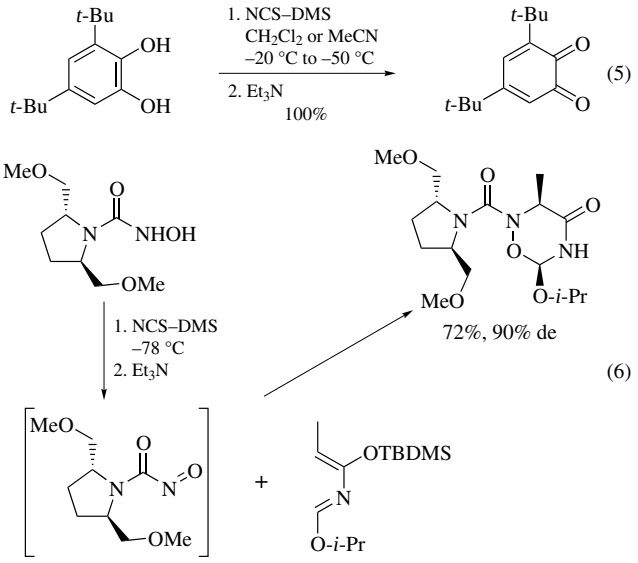
These reagents are also effective in the oxidation of *s,t*-1,2-diols to α-ketols (eq 3).[13] Metal-based reagents give carbon–carbon bond cleavage with such diols.



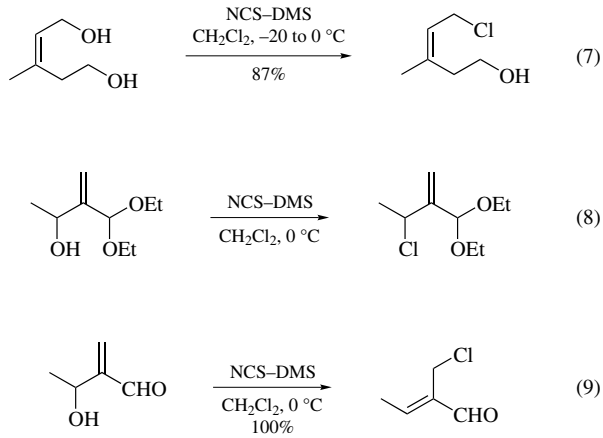
Oxidation of 1,3-keto alcohols or 1,3-diketones gives 1,3-diketo sulfonium ylides, which may be reduced to the 1,3-diketones (eq 4).[9]



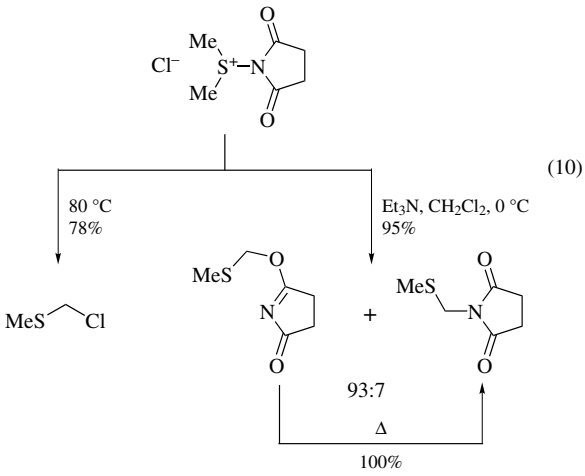
Catechols and hydroquinones are oxidized to quinones (eq 5),[3] and *N*-hydroxyureas are oxidized to nitroso compounds (eq 6).[4]



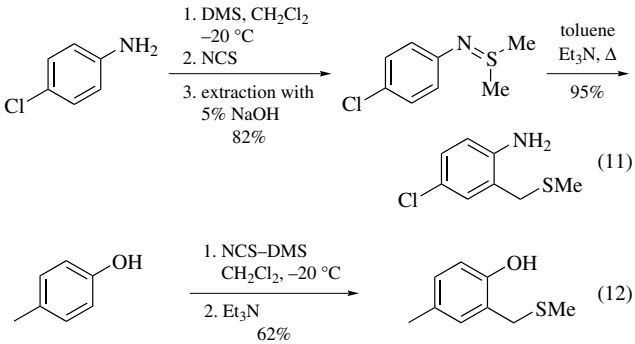
Halogenations. Allylic, benzylic, and cyclopropyl carbinyl alcohols are reported to undergo chlorination with or without allyl rearrangement, depending upon structure.[15] Thus primary and secondary allylic carbinols generally give the chlorides without rearrangement (eqs 7 and 8), whereas 2-formyl secondary allylic alcohols give the rearranged product (eq 9).[5]



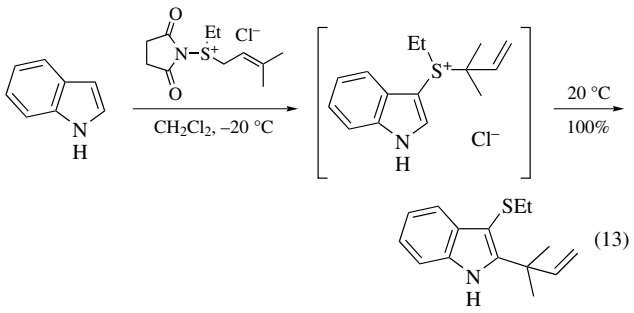
The NCS–dialkyl sulfide reagents are thermally labile, and depending on structure undergo a variety of transformations leading ultimately to α-chlorination of the sulfide (eq 10).[7]



***O*-Alkylation of Anilines and Phenols.** Treatment of anilines with NCS–DMS leads to sulfilimines, which may be converted to 2-alkylanilines (eq 11).[3] Similarly, phenols give directly the 2-substituted product (eq 12).[6]

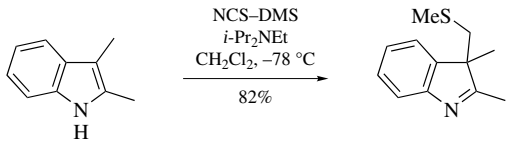


Other Alkylations. NCS and allylic sulfides react with 3-unsubstituted indoles at −20 °C to give initially 3-sulfonium salts which on warming to 20 °C rearrange to 2-allyl-3-thiomethylindoles (eq 13). These are readily desulfurized, either with or without concomitant reduction of the allylic double bond, to give 3-allyl or 3-alkyl substituted indoles.[8b,8c]



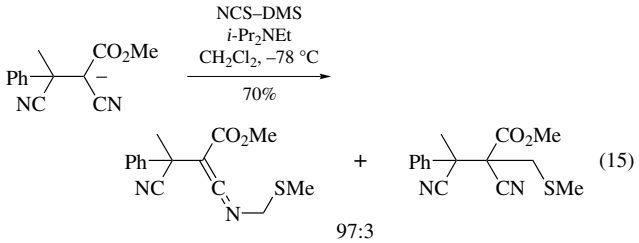
(13)

On the other hand, 3-alkyl-1*H*-indoles react with NCS–dialkyl sulfides in the presence of base to give 3-alkyl-3-alkylthioalkyl-3*H*-indoles (indolinenes, eq 14).[16]



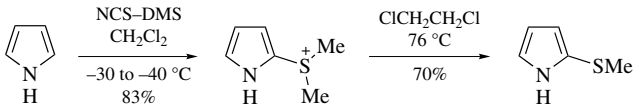
(14)

NCS–DMS reacts with cyanoacetate anions nearly exclusively at nitrogen to give *N*-alkylthiomethylketenimines (eq 15).[17]



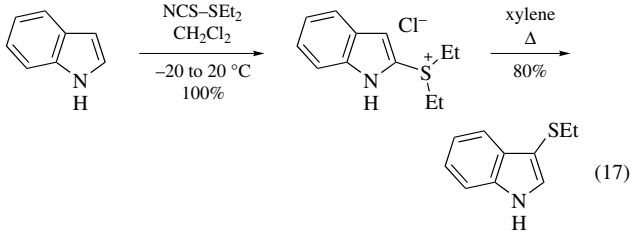
(15)

Thioalkylation. Treatment of pyrroles with NCS–DMS leads to 2-thiomethylpyrroles (eq 16). Indoles give 3-thioalkylindoles (eq 17).[8a–c]

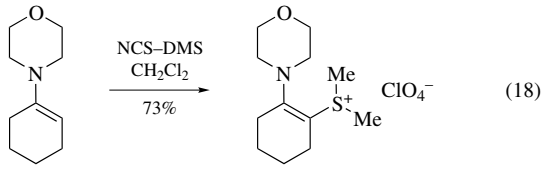


(16)

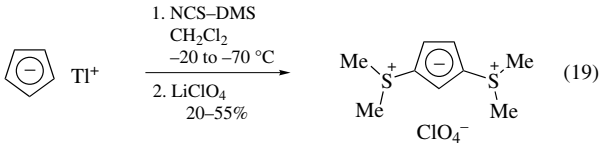
NCS–DMS reacts with enamines to give sulfonium salts (eq 18),[10a,10b] and with cyclopentadienyl anions to give bis- and tris-substituted sulfonium salts (eq 19).[10c]



(17)

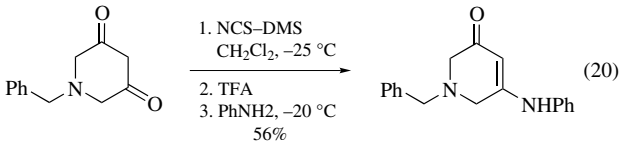


(18)



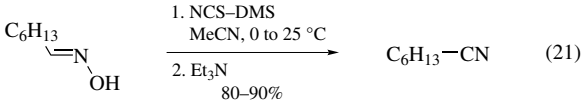
(19)

Dehydrations. While certain 1,3-diketones produce the sulfonium ylide, the treatment of *N*-acetylpiperidine-3,5-dione first with NCS–DMS and then with an amine in the presence of TFA resulted in the formation of the enaminone. The yields for this conversion were report to be significantly better than in the traditional method of azeotropic water removal (eq 20).[11a]



(20)

It was found during an attempt to produce *N*-methylthiomethyl nitrones that treatment of aldoximes with NCS–DMS resulted in high yields of nitriles (eq 21).[11b]



(21)

Related Reagents. Dimethyl Sulfoxide–Oxalyl Chloride; Dimethyl Sulfoxide–Phosgene; Dimethyl Sulfoxide–Triphosgene.

1. (a) Tidwell, T. T., *Org. React.* **1990**, *39*, 297. (b) Tidwell, T. T., *Synthesis* **1990**, 857. (c) Fisher, L. E.; Muchowski, J. M., *Org. Prep. Proced. Int.* **1990**, *22*, 399.
2. Marino, J. P.; Schwartz, A., *J. Chem. Soc., Chem. Commun.* **1974**, 812.
3. (a) Claus, P. K.; Rieder, W.; Hofbauer, P.; Vilsmaier, E., *Tetrahedron* **1975**, *31*, 505. (b) Claus, P. K.; Vycudilik, W.; Rieder, W., *Monatsh. Chem.* **1971**, *102*, 1571. (c) Gassman, P. G.; Gruetzmacher, G. D., *J. Am. Chem. Soc.* **1974**, *96*, 5487. (d) Gassman, P. G.; Parton, R. L., *Tetrahedron Lett.* **1977**, 2055.
4. Gouverneur, V.; Ghosez, L., *Tetrahedron Lett.* **1991**, *32*, 5349.
5. (a) Corey, E. J.; Kim, C. U.; Takeda, M., *Tetrahedron Lett.* **1972**, 4339. (b) Depezay, J. C.; Le Merrer, Y., *Tetrahedron Lett.* **1974**, 2751. (c) Depezay, J. C.; Le Merrer, Y., *Tetrahedron Lett.* **1974**, 2755.

6. (a) Gassman, P. G.; Amick, D. R., *Tetrahedron Lett.* **1974**, 889. (b) Gassman, P. G.; Amick, D. R., *Tetrahedron Lett.* **1974**, 3463. (c) Gassman, P. G.; Amick, D. R., *J. Am. Chem. Soc.* **1978**, *100*, 7611.
7. (a) Vilsmaier, E.; Sprugel, W., *Justus Liebigs Ann. Chem.* **1971**, *747*, 151. (b) Vilsmaier, E.; Dittrich, K. H.; Sprugel, W., *Tetrahedron Lett.* **1974**, 3601.
8. (a) Franco, F.; Greenhouse, R.; Muchowski, J. M., *J. Org. Chem.* **1982**, *47*, 1682. (b) Tomita, K.; Terada, A.; Tachikawa, R., *Heterocycles* **1976**, *4*, 729. (c) Tomita, K.; Terada, A.; Tachikawa, R., *Heterocycles* **1976**, *4*, 733. (c) Vilsmaier, E.; Sprugel, W.; Gagel, K., *Tetrahedron Lett.* **1974**, 2475. (d) Vilsmaier, E.; Troger, W.; Sprugel, W.; Gagel, K., *Chem. Ber.* **1979**, *112*, 2997.
9. (a) Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M., *Synthesis* **1988**, 178. (b) Katayama, S.; Watanabe, T.; Yamauchi, M., *Chem. Lett.* **1989**, 973. (c) Katayama, S.; Watanabe, T.; Yamauchi, M., *Chem. Pharm. Bull.* **1990**, *38*, 3314.
10. (a) Vilsmaier, E.; Sprugel, W.; Gagel, K., *Tetrahedron Lett.* **1974**, 2475. (b) Vilsmaier, E.; Troger, W.; Sprugel, W.; Gagel, K., *Chem. Ber.* **1979**, *112*, 2997. (c) Schlingensief, K. H.; Hartke, K., *Tetrahedron Lett.* **1977**, 1269.
11. (a) Tamura, Y.; Chen, L. C.; Fujita, M.; Kiyokawa, H.; Kita, Y., *Chem. Ind. (London)* **1979**, 668. (b) Dalgard, N. K. A.; Larsen, K. E.; Torssell, K. B. G., *Acta. Chem. Scand., Biochemistry* **1984**, *38*, 423.
12. McCormick, J. P., *Tetrahedron Lett.* **1974**, 1701.
13. Corey, E. J.; Kim, C. U.; Misco, P. F., *Org. Synth., Coll. Vol.* **1988**, *6*, 220.
14. Kim, K. S.; Cho, I. H.; Yoo, B. K.; Song, Y. H.; Hahn, C. S., *J. Chem. Soc., Chem. Commun.* **1984**, 762.
15. Murray, R. K., Jr.; Babiak, K. A., *Tetrahedron Lett.* **1974**, 311.
16. Katayama, S.; Watanabe, T.; Yamauchi, M., *Chem. Pharm. Bull.* **1992**, *40*, 2836.
17. Morel, G.; LeMoing-Orliac, M. A.; Khamsitthideth, S.; Foucaud, A., *Tetrahedron* **1992**, *38*, 527.

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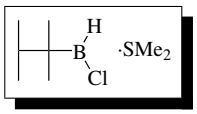
The Upjohn Company, Kalamazoo, MI, USA

Chloro(thexyl)borane–Dimethyl Sulfide



[75067-06-0] $C_8H_{20}BClS$ (MW 194.57)

InChI = 1/C6H14BCl.C2H6S/c1-5(2)6(3,4)7-8;1-3-2/h5,7H,1-4H3;1-2H3

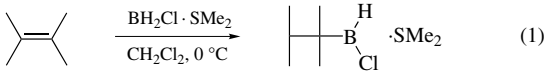
InChIKey = LANJRYQNHQMXPG-UHFFFAOYAT

(highly regioselective, monohydroborating agent for alkenes and alkynes, producing thexylalkylchloroboranes or thexylalkenylchloroboranes, respectively, which are synthetically useful intermediates;[1] reduces carboxylic acids to aldehydes;[2] reduces aldehydes and ketones to alcohols[2b])

Solubility: sol CH_2Cl_2, ether, and THF, but CH_2Cl_2 is the solvent of choice;[3] reacts rapidly with protic solvents.[2b]

Form Supplied in: prepared in situ.

Preparative Methods: most conveniently prepared from commercially available monochloroborane–dimethyl sulfide complex and 2,3-dimethyl-2-butene in CH_2Cl_2 (eq 1).[1a,3]

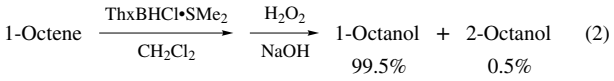


(1)

Analysis of Reagent Purity: analyzed by ^{11}B NMR and IR spectroscopy and by hydrogen evolution upon reaction with methanol.[3]

Handling, Storage, and Precautions: very reactive with oxygen and moisture and must be handled using standard techniques for handling air-sensitive materials.[4] Reported to be stable for at least two months when stored at 0 °C in CH_2Cl_2 solution under N_2.[2b]

Hydroboration of Alkenes and Alkynes. Chloro(thexyl)borane–dimethyl sulfide (ThxBHCl·SMe_2) in CH_2Cl_2 is a monohydroborating agent with exceptionally high regioselectivity.[1] This reagent has also been prepared in THF/Et_2O by the reaction of thexylborane–dimethyl sulfide with one equivalent of HCl.[5] However, CH_2Cl_2 is superior to Et_2O or THF as a solvent for hydroborations with this reagent.[3] Like disiamylborane (Sia_2BH) and 9-borabicyclo[3.3.1]nonane (9-BBN), ThxBHCl·SMe_2 has large steric requirements and reacts preferentially to add boron at the least hindered carbon atom of the carbon–carbon double or triple bond (eq 2).

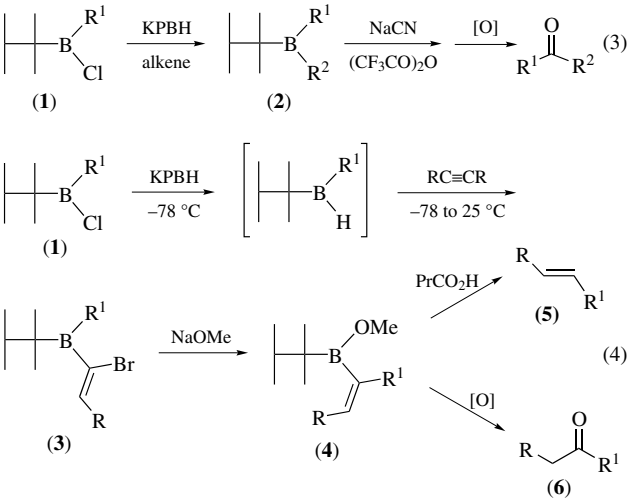


(2)

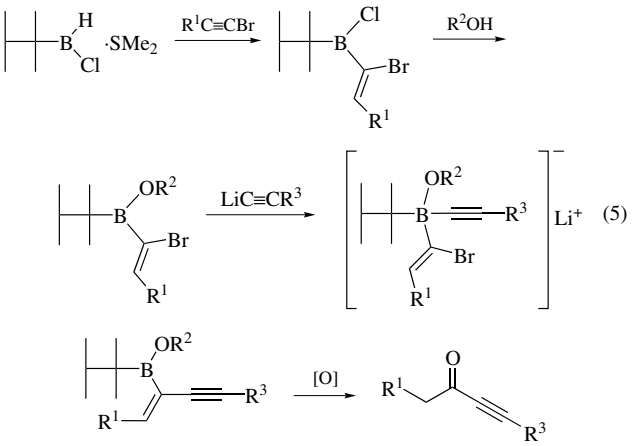
However, ThxBHCl·SMe_2 is more sensitive to electronic factors that either Sia_2BH or 9-BBN due to its higher Lewis acidity. Upon reaction with styrene followed by oxidation, ThxBHCl·SMe_2 gives a greater than 99:1 ratio of 2-phenylethanol to 1-phenylethanol, which is higher than any of the other common hydroborating agents.[1b] Internal alkenes are much less reactive than terminal alkenes toward hydroboration with ThxBHCl·SMe_2, and this reagent shows a much higher rate of reaction with *cis* disubstituted alkenes than with the *trans* isomers.[1c] Cyclohexenes and trisubstituted alkenes react more slowly with ThxBHCl·SMe_2 than do terminal or *cis* alkenes, and some redistribution of the reagent to ThxBH_2·SMe_2 and ThxBCl_2·SMe_2 can be observed with the long reaction times (>10 h) required for the reaction with relatively unreactive alkenes.[1b] ThxBHCl·SMe_2 reacts more rapidly with 1-hexyne or 3-hexyne than with 1-hexene.[6] Hydroborations of terminal alkynes with this reagent result in regioselective *syn* addition, affording the alkenylchloro(thexyl)borane in high yield.

Alkylchloro(thexyl)boranes (**1**) are useful intermediates in a variety of organic transformations. Reduction of these intermediates with potassium triisopropoxyborohydride (KPBH) in the presence of another alkene produces the mixed dialkylthexylborane (**2**), which can be converted to the corresponding unsymmetrical ketones (eq 3).[1b,7] Dialkylthexylboranes (**2**) are also produced by reaction of alkylchloro(thexyl)boranes (**1**) with equimolar amounts of organolithium or Grignard reagents.[5] Reduction of alkylchloro(thexyl)boranes at −78 °C with KPBH followed by addition of a 1-halo-1-alkyne and warming to room temperature affords *B*-(*cis*-1-halo-1-alkenyl)alkyl(thexyl)boranes (**3**) (eq 4). Treatment with sodium methoxide induces a selective migration of the alkyl group, resulting in the formation of *B*-(*trans*-1-alkyl-1-alkenyl)thexylborinate (**4**), which can be converted to the

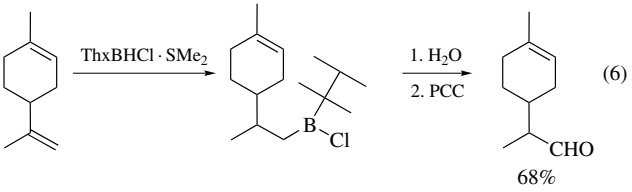
(*E*)-alkene (**5**) by protonolysis with isobutyric acid or to the ketone (**6**) by alkaline hydrogen peroxide oxidation.[8] The low migratory aptitude of the thexyl group results in only 2–7% of product where the thexyl group has migrated.



Hydroboration of 1-bromo-1-alkynes with chloro(thexyl)-borane leads to the synthesis of alkynyl ketones in 61–63% yields by the sequence of reactions[9] shown in eq 5. Sequential treatment of alkenylchloro(thexyl)boranes, which are formed by the reaction of chloro(thexyl)borane with alkynes, with lithium chloropropargylide and aldehydes affords 1,3-enynols or 1,2,4-trienols depending on the reaction conditions.[10]

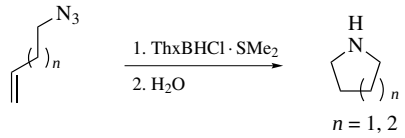


Alkylchloro(thexyl)boranes prepared from terminal alkenes can be hydrolyzed with one equivalent of water and then oxidized with pyridinium chlorochromate (PCC) to the corresponding aldehyde in moderate yields (eq 6).[11]



Reduction of Carboxylic Acids to Aldehydes. Aliphatic carboxylic acids are reduced rapidly (15 min) and aromatic carboxylic acids are reduced slowly (24 h) by chloro(thexyl)borane–dimethyl sulfide to the corresponding aldehydes.[2] Sodium bisulfite adducts were prepared to purify the aldehydes. Aliphatic aldehydes are isolated in 80–93% yields, and aromatic aldehydes are isolated in 46–78% yields.[2a] Alkoxy, nitro, cyano, halo, and ester functional groups are not reduced under these conditions.

Reductive Cyclization of ω-Azidoalkenes. Hydroboration of ω-azidoalkenes with chloro(thexyl)borane followed by hydrolysis affords, via an intramolecular reductive cyclization, the corresponding pyrrolidine (78%) or the piperidine (53%) (eq 7).[12]



1. (a) Brown, H. C.; Sikorski, J. A.; Kulkarni, S. U.; Lee, H. D., *J. Org. Chem.* **1980**, *45*, 4540. (b) Brown, H. C.; Sikorski, J. A.; Kulkarni, S. U.; Lee, H. D., *J. Org. Chem.* **1982**, *47*, 863. (c) Sikorski, J. A.; Brown, H. C., *J. Org. Chem.* **1982**, *47*, 872. (d) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic: London, 1988.
2. (a) Brown, H. C.; Cha, J. S.; Yoon, N. M.; Nazer, B., *J. Org. Chem.* **1987**, *52*, 5400. (b) Brown, H. C.; Nazer, B.; Cha, J. S.; Sikorski, J. A., *J. Org. Chem.* **1986**, *51*, 5264. (c) Brown, H. C.; Cha, J. S.; Nazer, B.; Yoon, N. M., *J. Am. Chem. Soc.* **1984**, *106*, 8001.
3. Brown, H. C.; Sikorski, J. A., *Organometallics* **1982**, *1*, 28.
4. Brown, H. C.; Kramer, G. W.; Levy, A.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley: New York, 1975; Chapter 9.
5. Zweifel, G.; Pearson, N. R., *J. Am. Chem. Soc.* **1980**, *102*, 5919.
6. Brown, H. C.; Chandrasekharan, J., *J. Org. Chem.* **1983**, *48*, 5080.
7. Kulkarni, S. U.; Lee, H. D.; Brown, H. C., *J. Org. Chem.* **1980**, *45*, 4542.
8. Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Lee, H. D.; Negishi, E.; Katz, J.-J., *J. Org. Chem.* **1986**, *51*, 5270.
9. Brown, H. C.; Bhat, N. G.; Basavaiah, D., *Synthesis* **1983**, 885.
10. Zweifel, G.; Pearson, N. R., *J. Org. Chem.* **1981**, *46*, 829.
11. Brown, H. C.; Kulkarni, S. U.; Rao, C. G.; Patil, V. D., *Tetrahedron* **1986**, *42*, 5515.
12. Jego, J. M.; Carboni, B.; Vaultier, M., *Bull. Soc. Chem. Fr. Part 2* **1993**, *129*, 554.

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Copper(II) Sulfate

$CuSO_4 \cdot 5H_2O$

[7758-99-8] $H_{10}CuO_9S$ (MW 249.68)

InChI = 1/Cu.H2O4S.5H2O/c;1-5(2,3)4;;;;;/h;(H2,1,2,3,4);5*1H2/q+2;;;;;;/p-2/fCu.O4S.5H2O/qm;-2;;;;;

InChIKey = JZCCFEFSEZPSOG-QLBZKNHHCL

(Lewis acid catalyst for alcohol dehydration,[1,31] acetonide formation,[6] acetal exchange,[9] ketone,[33] alcohol, and phenol[34] protection, *trans*-esterification of β-ketoesters,[36] imine[37] and oxime[38] formation, diazo-transfer,[39] cleavage of N–O bonds,[42]

hydrolysis of imines,[43] reductive amidation;[44] reagent for formation of copper carbenoids,[15] intramolecular and intermolecular cyclopropanations,[21,48] redox catalyst with potassium permanganate for oxidation of alcohols[25,53] and alkenes;[28,53] reagent for reduction of alkenes,[59] oximes,[60] and azides[61] with sodium borohydride or hydrazine; reductive removal of diazo group,[64] reductive dehydrazination,[65] and amino acid complexation[66]).

Physical Data: 110 °C, $-4H_2O$; 150 °C, $-5H_2O$; heating above 560 °C causes decomposition to CuO; *d* 2.28 g cm^{-3}.

Solubility: sol H_2O and methanol; slightly sol ethanol; insol acetone and ether; anhyd form sol H_2O, practically insol methanol and ethanol.

Form Supplied in: blue solid, widely available.

Drying: for certain applications, copper(II) sulfate must be used as an anhyd reagent; dehydration of $CuSO_4 \cdot 5H_2O$ can be accomplished by heating in an open porcelain dish at 275 °C for two days in a drying oven, stirring the sample several times during the drying period to break up any lumps; during this time the deep blue crystals are converted to an off-white powder.

Handling, Storage, and Precautions: $CuSO_4 \cdot 5H_2O$ can be stored and handled in the laboratory using normal laboratory methods; anhyd $CuSO_4$ is a powerful desiccant and must be stored out of contact with moisture, but can be weighed and transferred in the laboratory if atmospheric exposure is minimized; copper(II) sulfate is a strong irritant to the skin and mucous membranes.

Original Commentary

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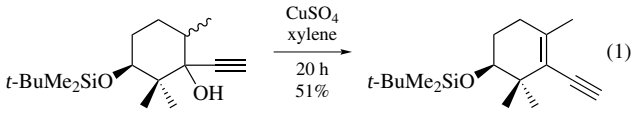
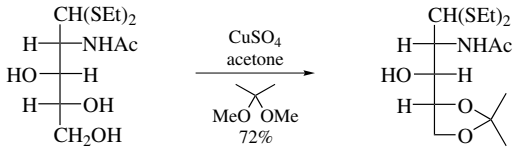
Introduction. The principal uses of $CuSO_4$ in organic synthesis stem from the chemical properties of Cu^{2+}. Firstly Cu^{2+} functions as a Lewis acid towards electron donor functions and can thus promote a variety of acid-catalyzed processes. Secondly Cu^{2+} reacts readily with diazo compounds to give carbenoid intermediates useful in subsequent addition reactions. Thirdly Cu^{2+} functions as an effective redox catalyst in several mixed oxidizing systems.

Lewis Acid Catalysis. Complexation of oxygen by Cu^{2+} makes an oxygen-containing functional group a much better leaving group. As such, the Cu^{2+} functions as a typical Lewis acid; however, anhyd $CuSO_4$ can be used effectively to promote a variety of reactions that would be adversely affected by significant amounts of water. The dehydration of alcohols by anhyd $CuSO_4$ is an excellent general method for the preparation of alkenes.[1] The alcohol (neat or in an inert solvent) is heated with 0.75–1.0 equiv of $CuSO_4$.[1–3] The copper sulfate can be used alone or supported on silica gel.[4] The method works well for benzylic, allylic, tertiary, and secondary alcohols, but is unsuitable for primary alcohols, which give the bis-ether rather than the alkene. The product mixtures are similar to those obtained in proton-catalyzed eliminations and suggest that carbocation intermediates are involved in the reaction. The method is mild and suitable for the formation of sensitive alkenes (eq 1).[5] See also copper(II) trifluoromethanesulfonate, phosphoric acid, potassium hydrogen sulfate, and sulfuric acid.



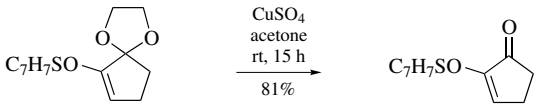
(1)

Anhyd copper sulfate is also an excellent catalyst for the formation of acetonides from glycols and acetone (eq 2).[6,7] Either 2,2-dimethoxypropane or 2-methoxypropene can sometimes improve the efficiency. The regiochemistry of the copper-catalyzed process is different from that found in the proton-catalyzed reaction.



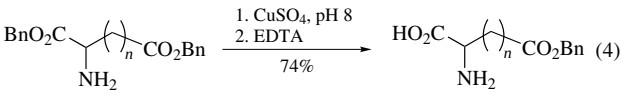
(2)

Acetonides can also be produced directly from epoxides and acetone using anhyd $CuSO_4$,[8] and acetal exchange can be used to deprotect ethylene glycol acetals under very mild conditions (eq 3).[9] Anhyd $CuSO_4$ has also been used as a Lewis acid catalyst for the removal of trityl protecting groups[10] and for Friedel–Crafts acylation of alkenes.[11]



(3)

Complexation of nitrogen by Cu^{2+} has been used to advantage in several cases. The selective hydrolysis of α-aminodiesters is guided by chelation to nitrogen and activation of the vicinal ester group (eq 4).[12] Cycloreversions of 2-azanorbornenes to give primary amines are catalyzed efficiently by copper sulfate (eq 5).[13] Copper sulfate (or other Cu^{2+} sources) facilitates the preparation of diimide from hydrazine by complexation with nitrogen.[14] See also copper(II) acetate.



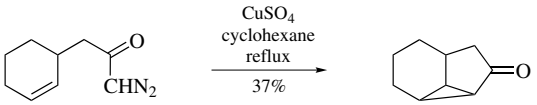
(4)

(5)

Copper Carbenoids. Copper(II) catalysts (as well as other copper species) promote the decomposition of diazo compounds and produce copper carbenoids as reactive intermediates. This is particularly useful for α-diazo carbonyl compounds, which then can add to unsaturated systems to give cyclopropanes.[15] In addition, chiral ligands can be attached to the copper, yielding cyclopropanes in high optical purities.[16,17]

Because intramolecular alkene additions are particularly favored with copper catalysts,[18] and because the low coordinating ability of the sulfate counterion is thought to contribute to an increased electrophilicity of the copper carbenoid when copper sulfate is used as the catalyst,[19] anhyd $CuSO_4$ has been used in

a variety of intramolecular cyclopropanations (eqs 6 and 7, for example).[20,21]



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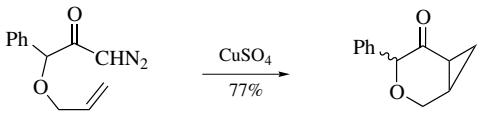
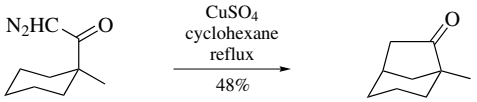


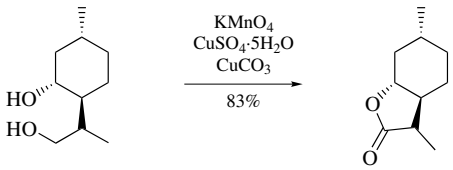
(7)

In the absence of double bonds, intramolecular insertion reactions into C–H bonds are observed (eq 8).[22] Recently, intramolecular insertion into the B–H bond of a carborane has been found to occur readily.[23] Anhyd $CuSO_4$ has also been used effectively to promote the formation of sulfur ylides in the reactions of diazo compounds and sulfides.[24] See also copper(I) acetylacetonate.



(8)

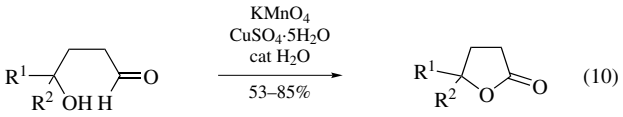
Redox Catalyst. Solid mixtures of $CuSO_4$ and oxidizing agents are useful for the oxidation of alcohols. For example, it was found that a solid mixture of potassium permanganate and copper sulfate pentahydrate oxidized secondary alcohols to ketones in high yields; however, primary alcohols were not oxidized under the same conditions.[25] This selectivity is quite unusual since under homogeneous conditions potassium permanganate vigorously oxidizes both primary and secondary alcohols. This selectivity is reversed by admixture of a solid base (either $CuCO_3$, copper(II) hydroxide, or potassium hydroxide) to the $KMnO_4$–$CuSO_4 \cdot 5H_2O$ oxidant (eq 9).[26]



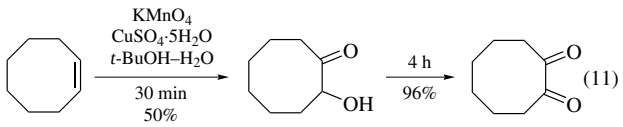
(9)

These results are rationalized on the basis of the heterogeneous oxidation which takes place on the surface of the solid oxidant. In the absence of an admixed base, secondary alcohols produce ketones which diffuse away from the oxidant surface. Primary alcohols produce carboxylic acids which are bound to the oxidizing surface, effectively blocking further reaction. Inclusion of the heterogeneous base results in neutralization of the acid product and reexposure of the oxidant surface; thus the normal selectivity is restored.

In these oxidations the use of hydrated $CuSO_4$ is mandatory. In fact, it was found that addition of catalytic amounts of water to the solid oxidant creates a more reactive oxidant for the synthesis of lactones from hydroxyaldehydes (eq 10).[27] Small quantities of aqueous *t*-butanol added to the solid oxidant permit the direct conversion of alkenes to α-hydroxy ketones and α-diketones (eq 11).[28] Normally, alkenes are inert to the solid oxidant. These differences are attributed to the formation of a thin aqueous phase on the surface of the oxidant (Ω phase) which facilitates phase transfer between the bulk liquid and the surface.



(10)



(11)

Copper sulfate in combination with ascorbic acid and oxygen has been used as a source of hydroxyl radicals to study the oxidation of dopamine.[29] Furthermore, copper sulfate has been used as a catalyst in the Ullmann reaction.[30] In both these cases, however, the copper sulfate merely serves as a source of Cu^{2+} which is reduced to a copper(I) species that is thought to be the key player in the process.

First Update

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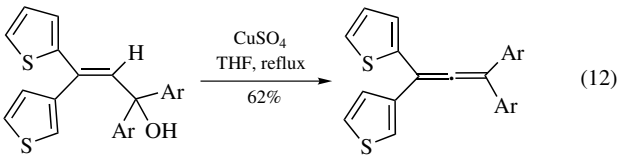
Introduction. Copper sulfate can be used as such or as a thin film on alumina. Uses of this handy reagent in organic synthesis emanate mainly from the characteristics of Cu(II) ions. For example, applications of $CuSO_4$ include: (i) use as a Lewis acid catalyst to activate oxygen and nitrogen containing functional groups capable of directing the attack of a nucleophile toward the adjacent electrophilic center; (ii) reaction with terminal acetylenes or diazo compounds to form copper acetylides or carbenoids, respectively, which are useful intermediates for further transformations; (iii) $CuSO_4$ by itself or coupled with $KMnO_4$ is a useful oxidizing agent, and $CuSO_4$ combined with sodium borohydride or hydrazine is a selective reducing agent; (iv) complexation with amino acids as a convenient means of protection.

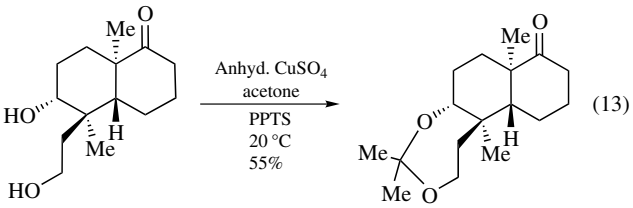
Lewis Acid Catalysis. Anhydrous copper sulfate continues to be used as an effective reagent for dehydration of alcohols to generate alkenes (eq 12).[31] The method is mild and tolerates several sensitive functional groups in the molecule.



(12)

Anhydrous $CuSO_4$ is a popular Lewis acid catalyst for protection of 1,2-diols as acetonoides. Even a 1,4-diol can be converted to its acetonide with this reagent (eq 13).[32] Similarly, anhydrous $CuSO_4$ can be used as a gentle catalyst for the generation of 1,3-dithiolanes from corresponding aliphatic, aromatic, or steroidal

ketones (eq 14).[33] In this respect, $CuSO_4$ is a better alternative to the more popular Lewis acid catalyst $BF_3{\cdot}Et_2O$.



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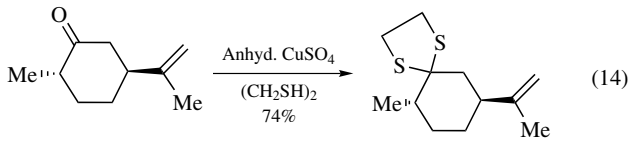
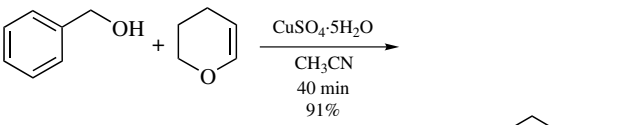


(14)

Catalytic amounts of $CuSO_4{\cdot}5H_2O$ can be used for protecting various phenols and alcohols as the corresponding THP ethers (eq 15).[34] Likewise, the alcohol and phenol functional groups can be efficiently acetylated with acetic anhydride under mild, solventless conditions (eq 16).[35] The catalyst can be recovered and reused in another reaction, which makes $CuSO_4$ a "green" reagent. Moreover, being a mild reagent, $CuSO_4$ does not affect functional groups such as alkenes, internal acetylenes, and acid sensitive protecting groups like THP and TBDMS ethers, acetonides, etc.



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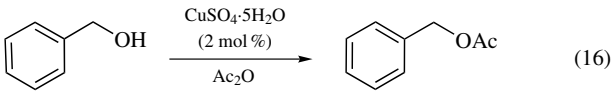
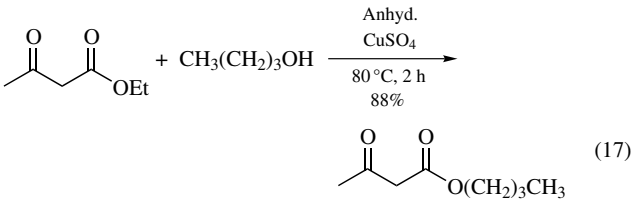


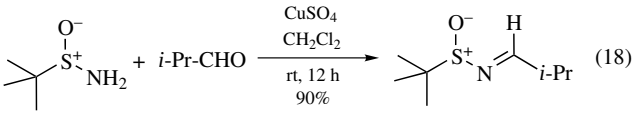
(16)

The acid-catalyzed transesterification of a β-keto ester with another alcohol is a difficult functional group inter-conversion. However, a catalytic amount of anhydrous $CuSO_4$ promotes smooth transesterification of methyl or ethyl β-keto esters with primary, secondary, and tertiary alcohols (eq 17).[36]



(17)

Stoichiometric amounts of anhydrous $CuSO_4$ can be employed in condensation reactions of sulfinamides (eq 18),[37] and hydroxylamines (eq 19)[38] with aldehydes to form the corresponding imines. The reaction works well in CH_2Cl_2 under biphasic conditions. In these reactions anhydrous $CuSO_4$ behaves as dehydrating agent and as Lewis acid catalyst.



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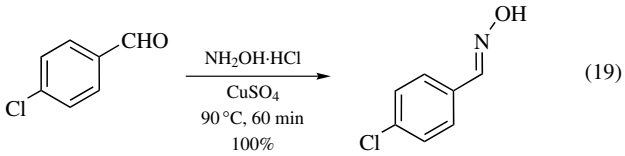
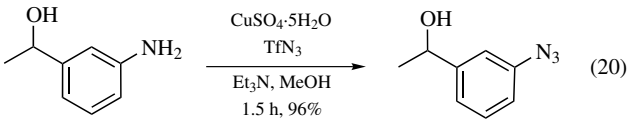
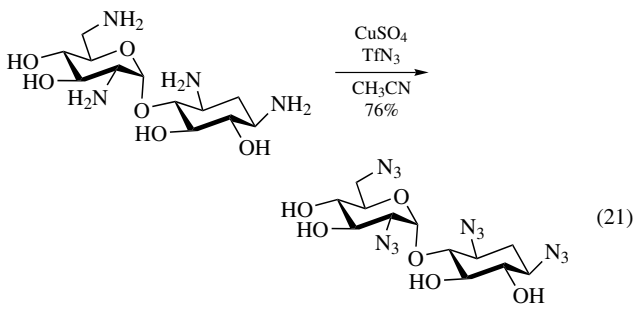


(19)

A catalytic amount of anhydrous $CuSO_4$ can be used for the conversion of aromatic amines to the corresponding azides by diazo transfer from trifluoromethanesulfonyl azide under mild conditions (eq 20).[39] In this intriguing reaction, complexation of nitrogen by Cu(II) ions in amines and further reaction with highly electrophilic trifluoromethanesulfonyl azide has been used to advantage for diazo-transfer.[40] Such a diazo-transfer reaction has wide applicability in "click" chemistry. The $CuSO_4$-catalyzed diazo transfer for converting amines to azides works well even on carbohydrate substrates (eq 21).[41]

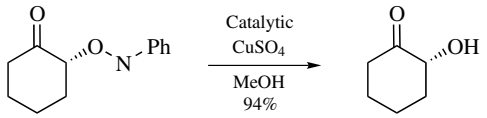


(20)



(21)

The ability of Cu(II) ions to complex with nitrogen in amines, activating various groups toward subsequent hydrolysis, continues to be explored for synthetic transformations. For example, the cleavage of N–O bond in chiral α-aminoloxy ketones to α-hydroxy ketones has been achieved with a catalytic amount of $CuSO_4$ (eq 22).[42] Similarly, iminosilacyclobutanes can be converted to anomeric mixtures of the corresponding hemiacetals (eq 23).[43] The Lewis acidic abilities of $CuSO_4$ can be efficiently exploited in the umpolung transformation of aromatic aldehydes to β-diketones via α-aminonitrile intermediates (eq 24).[44] In this multistep transformation, an aromatic aldehyde is initially converted to a α-aminonitrile. Alkylation of the α-aminonitrile with propargyl bromide followed by treatment with $CuSO_4{\cdot}5H_2O$ leads to a β-diketone. The role of $CuSO_4$ is for hydration of proporgyl group to acetonyl group and hydrolysis of α-aminonitrile to keto group.



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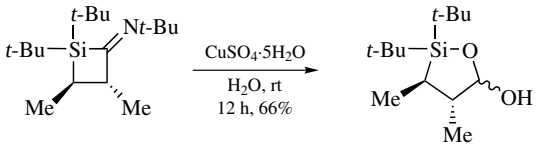

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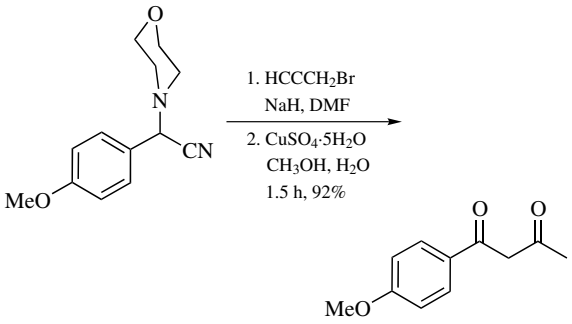
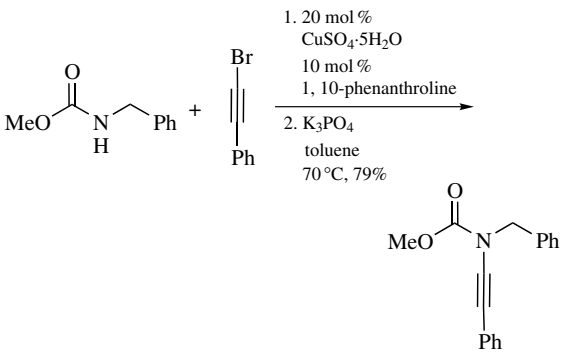
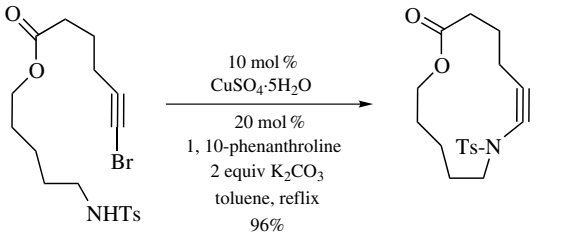


(24)

The $CuSO_4$–1,10-phenanthroline complex efficiently catalyzes amidation of alkynyl bromides to furnish ynamides, in both intermolecular and intramolecular manners (eq 25).[45a–c] This C–N bond forming reaction can be used for easy construction of macrocyclic ynamides (eq 26).[45a]

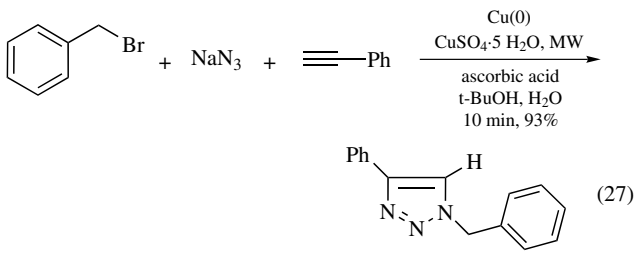


(25)



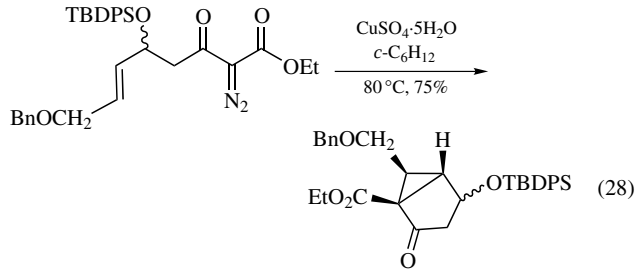
(26)

Synthesis of new materials based on "click chemistry" between a terminal acetylene and an azide unit to form a triazole continues to be of great interest.[46] The Click-cycloaddition requires Cu(I) species. The Cu(I) species can be generated easily by in situ reduction of $CuSO_4$ with ascorbic acid (eq 27).[47a–d] Application of microwave (MW) energy to promote this useful reaction has helped to reduce reaction times and increase reaction rates considerably.

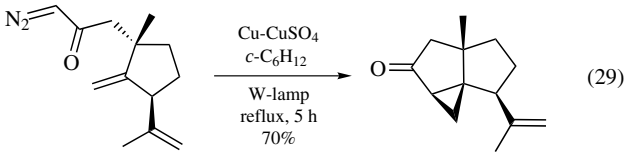


(27)

Copper Carbenoids. Several Cu(II) and Rh(II) salts catalyze decomposition of diazo compounds to produce metal carbenoids, which add to alkenes in an intra or intermolecular manner to generate cyclopropanes in high yields. The reagent anhydrous $CuSO_4$ is a cheaper and convenient alternative to other metal salts for accomplishing this reaction, particularly when intramolecular carbene cycloaddition is involved. The copper carbenoid intermediates generated next to a carbonyl group are elecrophilic in nature and they readily add to electron-rich double bonds to furnish cyclopropanes. Several complex synthetic schemes incorporate carbene–alkene cycloadditon as a key step in the construction of cyclic compounds. For example, the synthesis of carbocyclic nucleoside intermediates (eq 28),[48] the triquinane sesquiterpene (−)-cucumin H (eq 29),[49] (±)-albene,[50] and thujopsenes[51] incorporate $CuSO_4$-catalyzed intramolecular carbene–alkene cycloaddition as a key reaction.

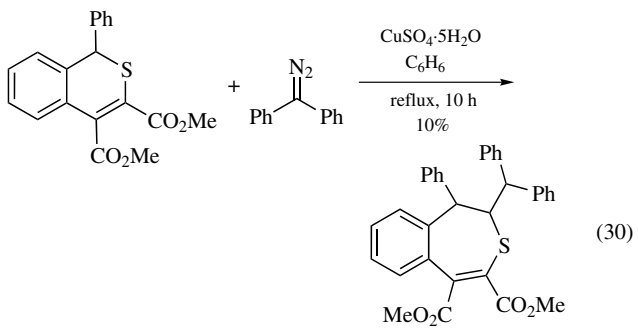


(28)



(29)

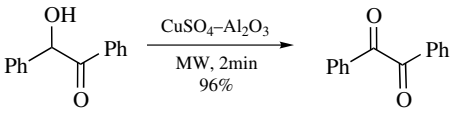
In the absence of double bonds, copper corbenoid intermediates can insert into weak C–H or C–S bonds (eq 30).[52]



(30)

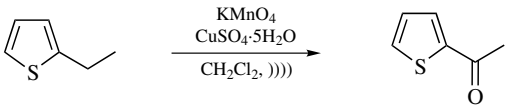
Oxidations. Copper sulfate is a mild reagent for the oxidation of reactive secondary alcohols to ketones. Solid mixture

of $CuSO_4{\cdot}5H_2O$ and benzoin loaded on Al_2O_3 affords vicinal diketones with in 2–3 min under MW irradiation. This protocol is effective for α-hydroxyl ketones but not for other secondary alcohols, pointing to the mild oxidation properties of $CuSO{\cdot}5H_2O$ (eq 31).[53]

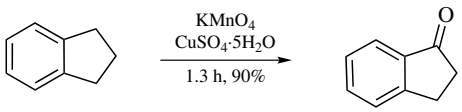


(31)

The solid mixture of $KMnO_4$ and $CuSO_4$ continuous to be a popular reagent system for oxidation of secondary alcohols to corresponding ketones; the reaction works well under the assistance of ultra sound (eq 32).[54] The reagent can even be used for oxidation of side chains in alkyl aromatic compounds to the corresponding ketones under solvent-free conditions (eq 33).[55]



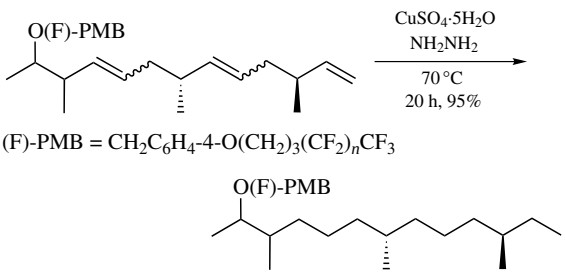
(32)



(33)

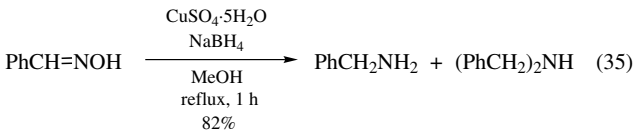
With this reagent thiols and primary aromatic amines can undergo oxidative coupling to give disulfides and diazenes, respectively.[54] Similarly sulfides can be oxidized to sulfones,[55] and strained cyclic alkenes to dialdehydes.[56] Under the heterogeneous conditions employed for these reactions, potassium permanganate behaves as a milder, selective oxidizing reagent. Some steroidal dienes were conveniently oxidized to ketones with this reagent system.[57a–b] It is believed that $CuSO_4{\cdot}5H_2O$ delivers the necessary amount of water required for the reaction and provides a solid support to $KMnO_4$ so that oxidation takes place on its surface under heterogeneous conditions.[58]

Reductions. $CuSO_4{\cdot}5H_2O$ is a useful reagent for transfer of hydrogen from donors to C–C double bonds under transfer hydrogenation conditions. For example, the combination of $CuSO_4$ and anhydrous hydrazine can be used for reduction of a triene to the corresponding alkane. Unlike the reduction with H_2/Pd-C, the hydrogenation by hydrazine and $CuSO_4{\cdot}5H_2O$ does not result in deprotection of a 4-methoxybenzyl ether. The reaction is believed to involve hydrogen adsorbed on finely divided copper metal (eq 34).[59]

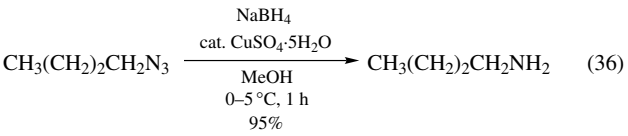


(34)

The combination of $CuSO_4{\cdot}5H_2O$ and sodium borohydride is useful for the reduction of oximes to primary and secondary amines (eq 35),[60] of aryl or alkyl azides to primary amines, and of acyl azides to amides (eqs 36 and 37).[61] In all these cases, in situ generated, finely divided colloidal copper metal with a large active metal surface area is expected to be responsible for reduction of the double bonds. For the reduction of azides to primary amines, the $CuSO_4{\cdot}5H_2O$ and sodium borohydride combination appears to be milder than H_2/Pd-C or H_2/Raney Ni, as reactive groups such has NO_2 survive the reaction conditions.

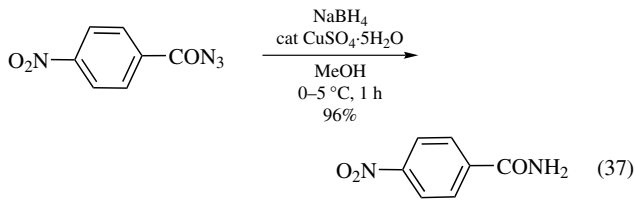


(35)

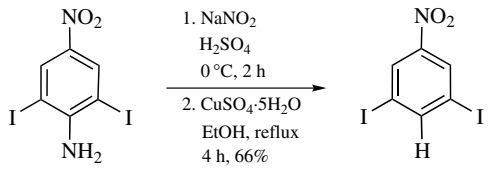


(36)

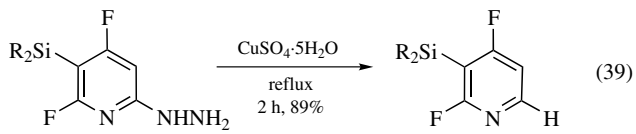
Reductive dediazotation with $CuSO_4$ is a classical reaction.[62] The diazo group, generated from primary amines with $NaNO_2$ and H_2SO_4 at 0 °C is treated with $CuSO_4{\cdot}5H_2O$ in ethanol to achieve overall reductive deamination (eq 38).[63] Similarly, reductive dehyrazination can be achieved with $CuSO_4$ (eq 39).[64] In this useful transformation, it is believed that complexation of the Cu(II) species with electron rich nitrogen in the hydrazine moiety followed by dehydrogenation leads to the formation of diazo intermediates, which undergo reductive removal of the functional group.



(37)

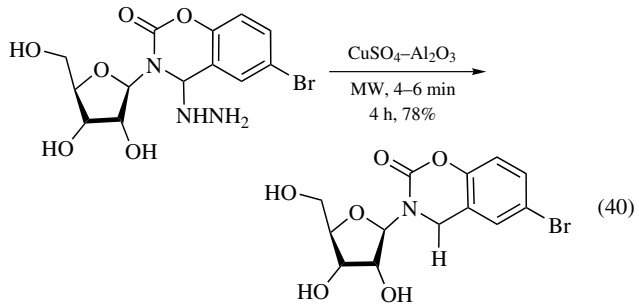


(38)



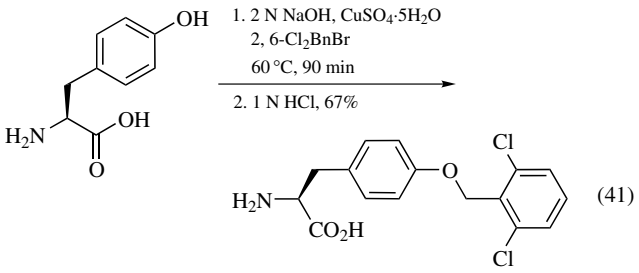
(39)

Reductive dehydrazinations of nucleosides can be carried out efficiently on $CuSO_4/Al_2O_3$ under MW irradiation (eq 40).[65]



(40)

Complexation with Amino Acids. Copper sulfate is an effective complexing agent for the protection of the amino acid group of an amino acid, permitting synthetic manipulations on its side chain to be carried out. For example, the phenolic hydroxyl of L-tyrosine can be converted to its 2,6-dichlorobenzyl ether by initially complexing with $CuSO_4 \cdot 5H_2O$ followed by treatment with 2,6-dichlorobenzyl bromide, and finally decomplexation with 1 N HCl to furnish L-tyr(2,6-Cl_2Bn)OH (eq 41).[66]



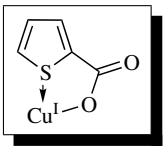
(41)

Related Reagents. Potassium Permanganate–Copper(II) Sulfate.

1. Hoffman, R. V.; Bishop, R. D.; Fitch, P. M.; Hardenstein, R., *J. Org. Chem.* **1980**, *45*, 917.
2. Francis, G. W.; Berg, J. F., *Acta Chem. Scand.* **1977**, *31B*, 721.
3. Shankaranarayana, K. H.; Ayyar, K. S., *Chem. Scr.* **1979**, *48*, 683.
4. Nishiguchi, T.; Machida, N.; Yamamoto, E., *Tetrahedron Lett.* **1987**, *28*, 4565.
5. Mori, K.; Watanabe, H., *Tetrahedron* **1986**, *42*, 273.
6. Miljkovic, M.; Hagel, P., *Carbohydr. Res.* **1983**, *111*, 319.
7. Morgenlie, S., *Carbohydr. Res.* **1975**, *41*, 77.
8. Hanzlik, R. P.; Leinwetter, M., *J. Org. Chem.* **1978**, *43*, 438.
9. Hulce, M.; Mallomo, J. P.; Frye, L. L.; Kogan, T. P.; Posner, G. H., *Org. Synth., Coll. Vol.* **1990**, *7*, 495.
10. Randazzo, G.; Capasso, R.; Cicala, M. R.; Evidente, A., *Carbohydr. Res.* **1980**, *85*, 298.
11. Morel-Fourier, C.; Dulcère, J. P.; Santelli, M., *J. Am. Chem. Soc.* **1991**, *113*, 8062.
12. Prestidge, R. L.; Harding, D. R. K.; Battesby, J. E.; Hancock, W. S., *J. Org. Chem.* **1975**, *40*, 3287.
13. Grieco, P. A.; Clark, J. D., *J. Org. Chem.* **1990**, *55*, 2271.
14. Ohno, M.; Okamoto, M., *Org. Synth., Coll. Vol.* **1973**, *5*, 281.
15. Burke, S. D.; Grieco, P. A., *Org. React.* **1980**, *26*, 361.
16. Baldwin, J. E.; Barden, T. C., *J. Am. Chem. Soc.* **1984**, *106*, 6364.
17. Matsuura, I.; Ueda, T.; Murakami, N.; Nagai, S.; Sakakibara, J., *J. Chem. Soc., Chem. Commun.* **1991**, 1688.
18. Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P., *J. Org. Chem.* **1980**, *45*, 5020.
19. Maryanoff, B. E., *J. Org. Chem.* **1979**, *44*, 4410.
20. Russell, G. A.; McDonnell, J. J.; Whittle, P. R.; Givens, R. S.; Keske, R. C., *J. Am. Chem. Soc.* **1971**, *93*, 1452.
21. Hon, Y. S.; Chang, R. C., *Heterocycles* **1991**, *32*, 1089.
22. Agosta, W. C.; Wolff, S., *J. Org. Chem.* **1975**, *40*, 1027.
23. Wu, S.; Jones, M., Jr., *Inorg. Chem.* **1986**, *25*, 4802.
24. Benati, L.; Montevecchi, P. C.; Spagnolo, P., *J. Chem. Soc., Perkin Trans. 1* **1982**, 917.
25. Menger, F. M.; Lee, C., *J. Org. Chem.* **1979**, *44*, 3446.
26. Jefford, C. W.; Wang, Y., *J. Chem. Soc., Chem. Commun.* **1988**, 634.
27. Baskaran, S.; Islam, I.; Vankar, P. S.; Chandrasekaran, S., *J. Chem. Soc., Chem. Commun.* **1990**, 1670.
28. Baskaran, S.; Das, J.; Chandrasekaran, S., *J. Org. Chem.* **1989**, *54*, 5182.
29. Ito, S.; Takimura, M.; Sasaki, K., *Chem. Lett.* **1993**, 461.
30. Lindley, J., *Tetrahedron* **1984**, *40*, 1433.
31. Kurata, H.; Mondeh, M.; Kawase, T.; Oda, M., *Tetrahedron Lett.* **1998**, *39*, 7135.
32. Patin, A.; Kanazawa, A.; Philouze, C.; Greene, A. E., *J. Org. Chem.* **2003**, *68*, 3831.
33. Nayak, A.; Nanda, B.; Das, N. B.; Sharma, R. P., *J. Chem. Res. (S)* **1994**, 100.
34. Khan, A. T.; Choudhary, H. L.; Ghosh, S., *Tetrahedron Lett.* **2004**, *45*, 7891.
35. Heravi, M. M.; Behbahani, F. K.; Zadsirjan, V.; Oskooie, H., *J. Braz. Chem. Soc.* **2006**, *17*, 1045.
36. Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S., *Synth. Commun.* **2001**, *31*, 2063.
37. Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A., *J. Org. Chem.* **1999**, *64*, 1278.
38. Sharghi, H.; Sarvari, M. H., *Synlett* **2001**, *1*, 99.
39. Liu, Q.; Tor, Y., *Org. Lett.* **2003**, *5*, 2571.
40. Nyffeler, P. T.; Liang, C. H.; Koeller, K. M.; Wong, C. H., *J. Am. Chem. Soc.* **2002**, *124*, 10773.
41. Yan, R. B.; Yang, F.; Wu, Y.; Zhang, L. H.; Ye, X. S., *Tetrahedron Lett.* **2005**, *46*, 8993.
42. Momiyama, N.; Yamamoto, H., *J. Am. Chem. Soc.* **2003**, *125*, 6038.
43. Nguyen, P. T.; Palmer, W. S.; Woerpel, K. A., *J. Org. Chem.* **1999**, *64*, 1843.
44. Mahalingam, S. M.; Aidhen, I. S., *J. Org. Chem.* **2006**, *71*, 349.
45. (a) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenneimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R., *J. Org. Chem.* **2006**, *71*, 4170. (b) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M; Vera, E. L., *Org. Lett.* **2004**, *6*, 1151. (c) Zhang, X.; Hsung, R. P.; You, L., *Chem. Commun.* **2006**, *4*, 2679.
46. Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Eycken, E. V., *Org. Lett.* **2004**, *6*, 4223.
47. (a) Zhu, L.; Lynch, V. M.; Anslyn, E. V., *Tetrahedron*, **2004**, *60*, 7267. (b) Jorlemon, M. J.; O' Reilly, R. R.; Hawker, C. J.; Wooley, K. L., *J. Am. Chem. Soc.* **2005**, *127*, 16892. (c) Parrish, B.; Breitenkamp, R. B.; Emrick, T. J., *Am. Chem. Soc.* **2005**, *127*, 7404. (d) Malkoch, M.; Vestberg, R.; Gupta, N.; Mespouille, L.; Dubois, P.; Mason, A. F.; Hedrick, J. L.; Liao, Q.; Frank, C. W.; Kingsbury, K.; Hawker, C. J., *Chem. Commun.* **2006**, 2774.
48. Comin, M. J.; Parrish, D. A.; Deschamps, J. R.; Marquez, V. E., *Org. Lett.* **2006**, *8*, 705.
49. Srikrishna, A.; Dethe, D. H., *Org. Lett.* **2003**, *5*, 2295.
50. Srikrishna, A.; Nagaraju, S., *Phytochemistry* **1995**, *40*, 1699.
51. Srikrishna, A.; Anebouselvy, K., *J. Org. Chem.* **2001**, *66*, 7102.
52. Okuma, K.; Koga, Y.; Kojima, K.; Shioji, K.; Matsuyama, H.; Yakomori, Y., *J. Org. Chem.* **2000**, *65*, 2090.

53. Varma, R. S.; Kumar, D.; Dahiya, R., *J. Chem. Res.* (*S*) **1998**, 324.
54. MaČiarova, M.; Toma, S.; Heribanovà, A., *Tetrahedron* **2000**, *56*, 8561.
55. Shaabani, A.; Lee, D. G., *Tetrahedron Lett.* **2001**, *42*, 5833.
56. Goksu, S.; Altondas, R.; Sutbeyaz, Y., *Synth. Commun.* **2000**, *30*, 1615.
57. (a) Hanson, J. R.; Hitchcock, P. B.; Nagaratnam, S. J., *Chem. Res.* (*S*) **1999**, 22. (b) Parish, E. J.; Li, S., *J. Org. Chem.* **1996**, *61*, 5665.
58. Noureldin, N. A.; Zaho, D.; Lee, D. G., *J. Org. Chem.* **1997**, *62*, 8767.
59. Dandapani, S.; Jeske, M.; Curran, D. P., *J. Am. Chem. Soc.* **2005**, *70*, 9447.
60. Rao, H. S. P.; Bharathi, B., *Ind. J. Chem.* **2002**, *14B*, 1072.
61. Rao, H. S. P.; Siva, P., *Synth. Commun.* **1994**, *24*, 549.
62. Kornblum, N., *Org. React.* **1944**, *2*, 262.
63. Brink, G. J.; Vis, J. M.; Arends, I. W. C. E.; Sheldon, R. A., *Tetrahedron* **2002**, *58*, 3977.
64. Schlosser, M.; Bobbio, C.; Rausis, T., *J. Org. Chem.* **2005**, *70*, 2494.
65. Yadav, L. D. S.; Yadav, B. S.; Rai, V. K., *Tetrahedron Lett.* **2004**, *45*, 5351.
66. Casimir, J. R.; Tourwé, D.; Iterbeke, K.; Guicjard, G.; Briand, J. P., *J. Org. Chem.* **2000**, *65*, 6487.

Copper, (2-Thiophenecarboxylato-$\kappa O_2, \kappa S_1$)



[68986-76-5] $C_5H_3CuO_2S$ (MW 190.69)

InChI = 1/C5H4O2S.Cu/c6-5(7)4-2-1-3-8-4;/h1-3H,(H,6,7);/q;+1/p-1/fC5H3O2S.Cu/q-1;m

InChIKey = SFJMFSWCBVEHBA-MFTWZWOHCC

(reagent used as additive for the formation of C–C, C–N, and C–O bonds)

Physical Data: not available.

Solubility: insoluble in most organic solvents.

Form Supplied in: tan-brown powder, it contains small amounts of Cu(I) oxide.

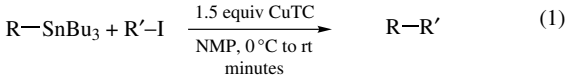
Purification: wash under nitrogen with MeOH and then with ethyl ether; once the solvents are removed, the reagent is stable.

Handling, Storage, and Precautions: the compound is stable and can be handled in air with no special precautions although it is recommended to store it under nitrogen. It is irritating to the eyes, respiratory system, and skin and should be handled in a well-ventilated fume hood. Avoid contact with strong oxidizing agents.

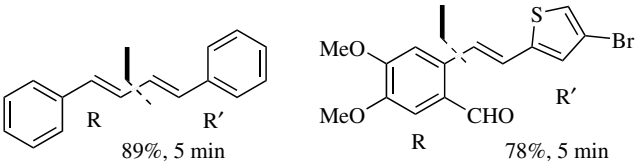
Promoter and Catalyst for the Formation of C–C bonds.

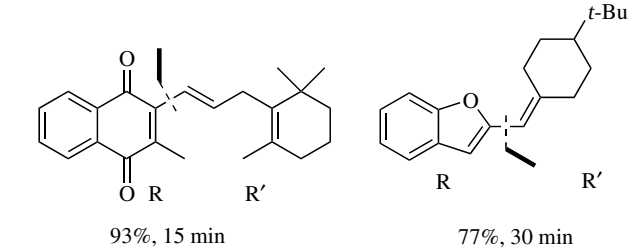
(a) *Promoter of Cross-Coupling Reactions*. Since the introduction of copper(I) 2-thiophenecarboxylate (CuTC) in 1996 by Allred and Liebeskind, this reagent has found a wide range of applications. In their first report, the Liebeskind group disclosed the CuTC-mediated cross-coupling of organostannanes with organic iodides at or below room temperature (eq 1).[1]

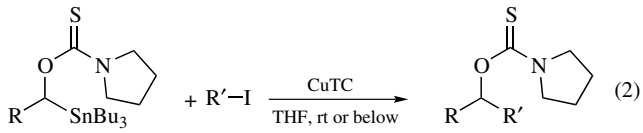
The reaction is carried out under very mild conditions in *N*-methyl-2-pyrrolidinone (NMP) and is finished within minutes to give a family of 16 derivatives in good to excellent yields. Under similar conditions, Falck et al. have reported the cross-coupling of protected α-hydroxystannanes with vinyl iodides (eq 2).[2]



(1)



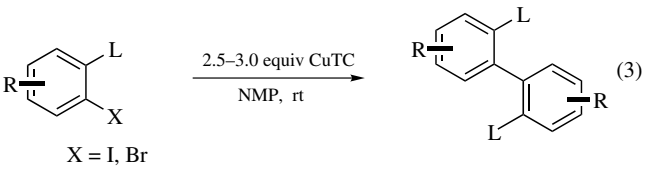




(2)

R′ = vinyl, aryl, heteroaryl 25 examples 60–92%

Aryl, heteroaryl, and alkenyl halides participate in Ullman-like reductive couplings in the presence of 2.5–3.0 equiv of CuTC at ambient temperature in NMP. Aryl iodides and bromides dimerize as long as there is an *ortho*-ligating substituent (eq 3).[3]



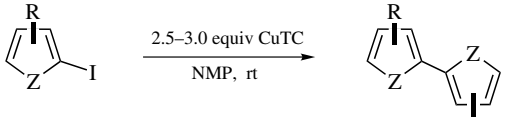
(3)

X = I, Br

L = COOMe, NO_2, C=S(NMe_2), NHCOMe, CH_2OH, etc.

13 examples, 41–99%

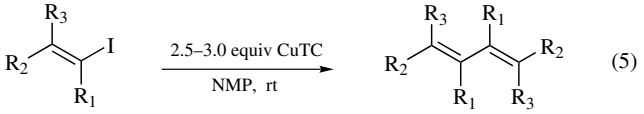
Such a requirement is not necessary for 2-iodoheteroaromatic and alkenyl substrates (eqs 4 and 5).



(4)

Z = —S—, —C(Me)=N—, —NCO_2Et

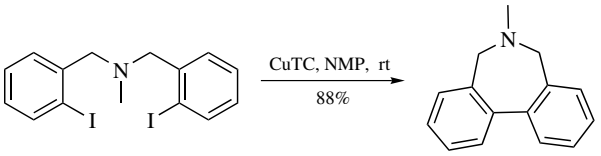
3 examples, 60–77%



(5)

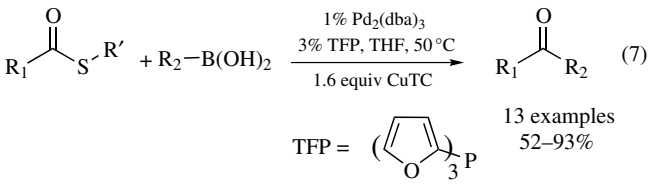
7 examples, 78–92%

The usefulness of this protocol was further demonstrated by its intramolecular version (eq 6).



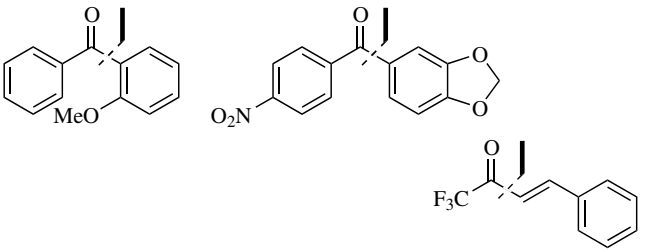
(6)

In combination with catalytic amounts of Pd, CuTC has given rise to novel cross-coupling reactions *under mild and neutral* conditions that have furnished a number of very useful organic building blocks.[4] Thus, an unprecedented cross-coupling of thiol esters with aryl and alkenylboronic acids in the presence of a catalytic amount of Pd(0) and 1.6 equiv of CuTC furnished a wide variety of aryl ketones *under baseless conditions* (eq 7).[5]

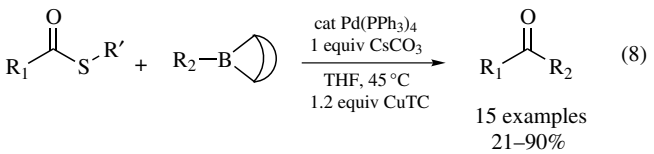


(7)

13 examples
52–93%

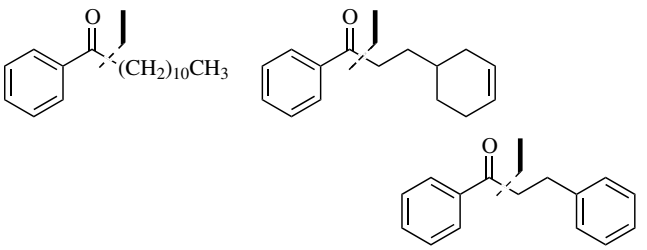


Following this initial ketone synthesis, other variants of the same process were documented in the literature. For instance, thiol esters also react with *aliphatic* organoboron reagents under similar conditions. However, the presence of a full equivalent of Cs_2CO_3 was needed to improve the yields (eq 8).[6]

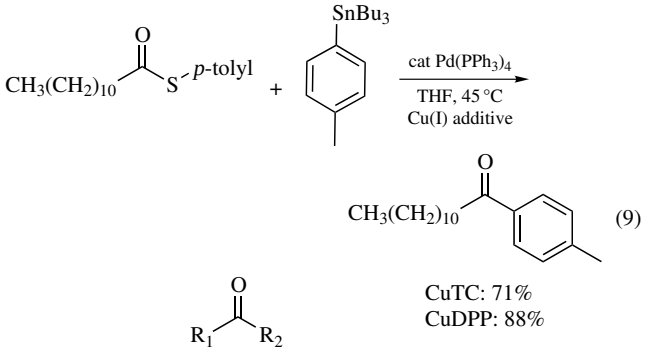


(8)

15 examples
21–90%



In another example, it was found that, in addition to boronic acids, organostannanes also participate in the Liebeskind ketone synthesis. In this reaction, however, Cu(I) diphenylphosphinate (CuDPP) gave higher yields (eq 9).[7]

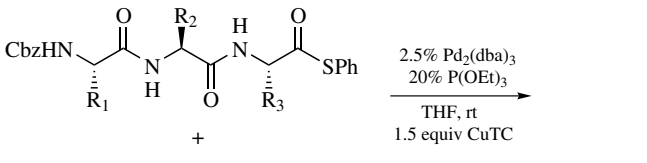


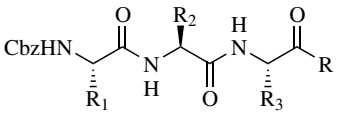
(9)

CuTC: 71%
CuDPP: 88%

17 examples
67–96%
with CuDPP

A relevant extension of this method consists of the synthesis of *N*-protected peptidyl ketones. This procedure takes place at room temperature under nonbasic conditions with high functional group tolerance. Additionally, the products are prepared with high enantiopurity.[8] For the reaction to work smoothly, triethylphosphite has to be used as a supporting ligand to suppress the Pd-catalyzed decarbonylation–β-elimination of the α-amino thiol esters (eq 10).



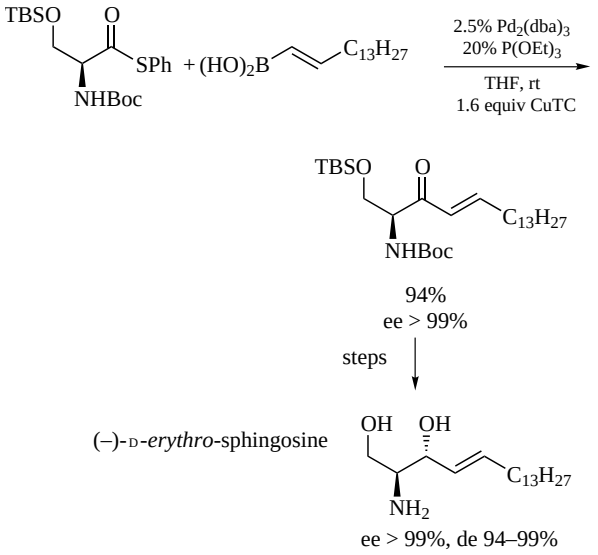


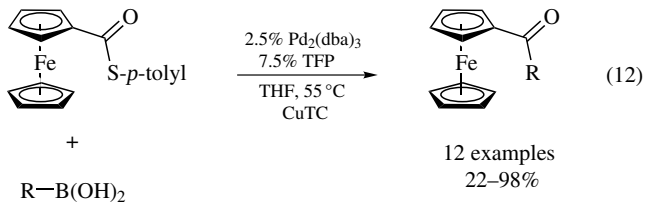
(10)

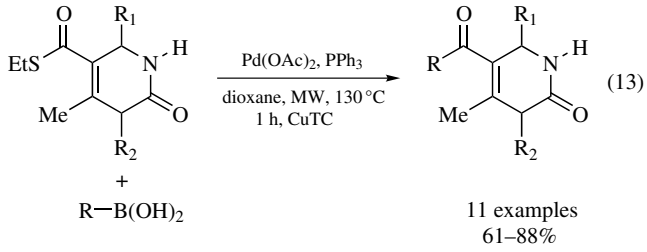
9 examples
62–94%
91–99% de

A direct application of this method resulted in a scalable synthesis of (−)-D-*erythro*-sphingosine (eq 11).[9]

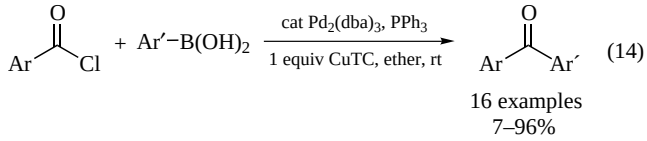
Other related applications include the synthesis of aryl ferrocenyl ketones (eq 12)[10] and that of 5-aroyldihydropyrimidones using microwaves under more forcing conditions (eq 13).[11–13]



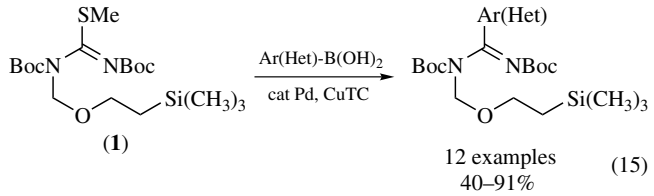




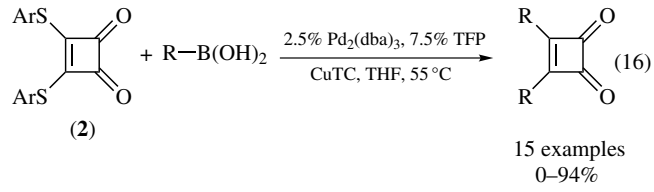
In addition to stable thiol esters, acid chlorides can be used as well in the Pd-catalyzed, CuTC-promoted synthesis of ketones with boronic acids (eq 14).[14]



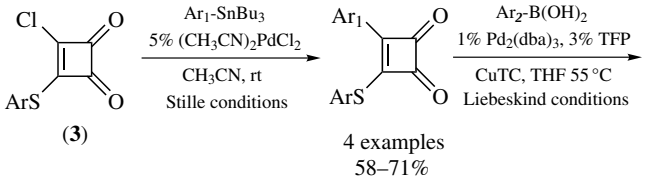
Similarly, protected aryl and heteroaryl amidines were prepared starting from SEM-protected thiopseudourea (**1**). Treatment of (**1**) with aryl and heteroarylboronic acids furnished the desired products in good to excellent yield (eq 15).[15]

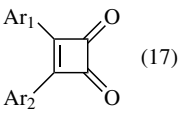


Arylthiocyclobutenediones may be considered as vinylogous thiol esters. As such, they were expected to participate in the Liebeskind–Srogl cross-coupling. Thus, (**2**) was exposed to a variety of boronic acids under the Liebeskind conditions to give the corresponding symmetrical cyclobutenediones (eq 16).[16]



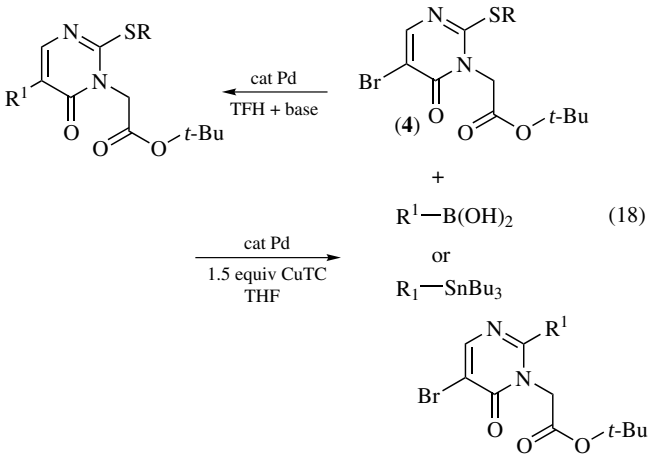
The C–S bond will be activated toward cross-couplings as long as both Pd and a copper(I)-carboxylate are present. On the contrary the C–X bond (X = halogen, sulfonate, etc.) can be activated in the presence of Pd, under "copperless" conditions. This selective activation allows the preparation of bifunctional substrates with "orthogonal" reactivity, that is, compounds that, upon judicious selection of reaction conditions, can be made to react at one center or another at will. One example of orthogonal reactivity was displayed by chlorothiocyclobutenedione (**3**) whereby the C–Cl bond was activated under the regular Stille conditions and then the C–S bond was activated under the Liebeskind conditions to yield nonsymmetric cyclobutenediones (eq 17).[17]



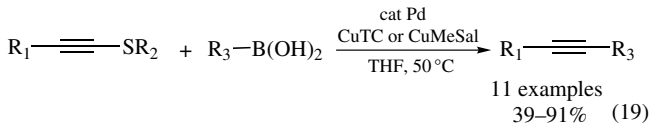


In another report, bromothiopyrimidones (**4**) were selectively functionalized by choosing the appropriate reaction conditions (eq 18).[18]

Another successful application of CuTC is the synthesis of substituted alkynes under nonbasic conditions. In this case, Cu^I 3-methylsalicylate (CuMeSal) was equally effective in promoting the reaction (eq 19).[19]

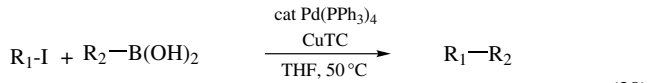


(18)



(19)

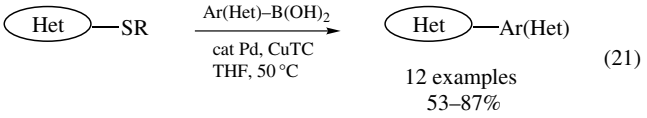
CuTC also promotes the nonbasic version of the Suzuki cross-coupling.[20] It was observed that both aryl and alkenyl iodides reacted smoothly with a variety of aryl, heteroaryl, and alkenylboronic acids in the presence of a Pd catalyst and an equivalent of CuTC at room temperature (eq 20). Bromo, chloro, and triflate derivatives failed to couple.



(20)

R_1 = aryl, alkenyl
R_2 = aryl, heteroaryl, alkenyl

π-Deficient heteroaromatic thioethers participate in the Pd-catalyzed cross-coupling with aryl and heteroarylboronic acids in the presence of 1.3 equiv of CuTC; no base was required. A family of 12 compounds with various functional groups was prepared in this manner (eq 21).[21]

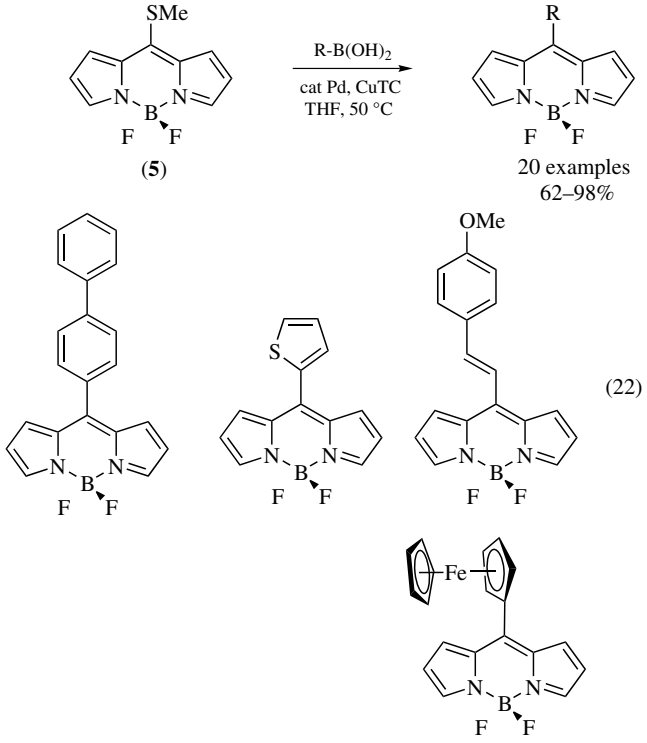


(21)

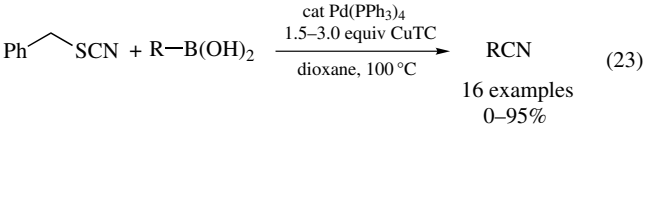
More recently, a general and efficient synthesis of borondipyrromethene (BODIPY) dyes was reported.[22] Starting from thiomethylbodipy (**5**), a wide variety of *meso*-substituted aryl, heteroaryl, alkenyl, and organometallic BODIPY derivatives were prepared (eq 22).

Boronic acids were cyanated under cyanide-free reaction conditions. Benzylthiocyanate served as cyanide equivalent and reacted with aryl, heteroaryl, and alkenyl boronic acids in the presence of a Pd catalyst and 1.5–3.0 equiv of CuTC (eq 23).[23]

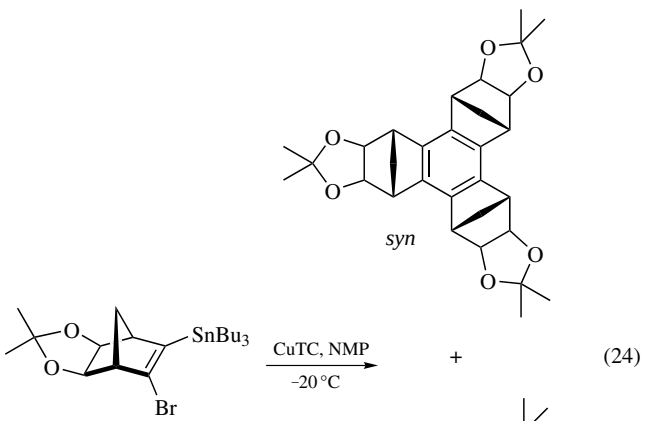
CuTC has been shown to promote the cyclotrimerization of bicyclic *vic*-bromostannylalkenes (eq 24).[24]



(22)

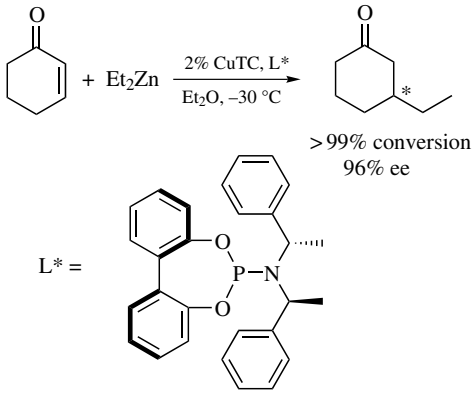


(23)



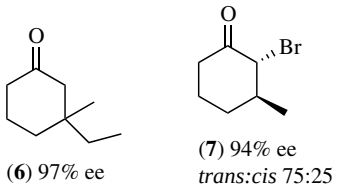
(24)

(b) *Catalyst for Conjugate Additions*. CuTC has also been used as a catalyst for asymmetric conjugate additions in conjunction with chiral ligands (eq 25).[25]

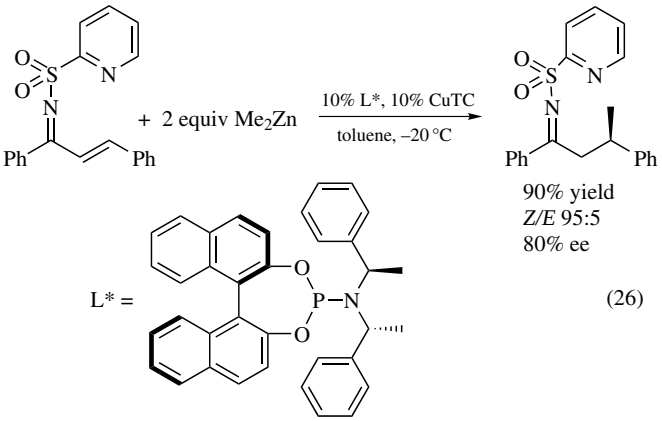


(25)

Under similar reaction conditions, other enantiomerically enriched keto derivatives have been prepared, for example, (**6**) and (**7**).[26,27]

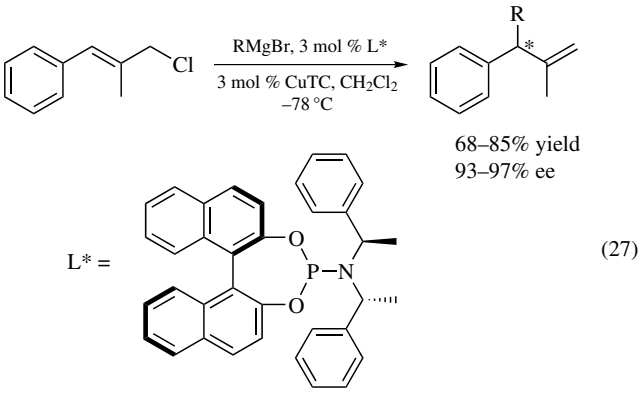


(2-Pyridyl)sulfonyl imines of chalcones also serve as substrates for enantioselective conjugate additions of dialkylzinc reagents catalyzed by CuTC (eq 26).[28]



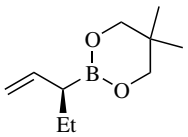
(26)

(c) *Catalyst for Asymmetric Allylic Alkylation Reactions*. Addition of Grignard reagents to β-disubstituted allylic chlorides in the presence of catalytic amounts of a chiral phosphoramidite and CuTC yielded the corresponding alkylated allylic substrates with high ee (eq 27).[29,30]



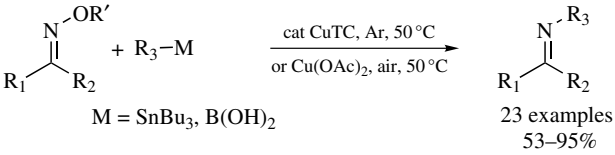
(27)

α-Substituted allylboronates (**8**) were also prepared via a similar process.[31]



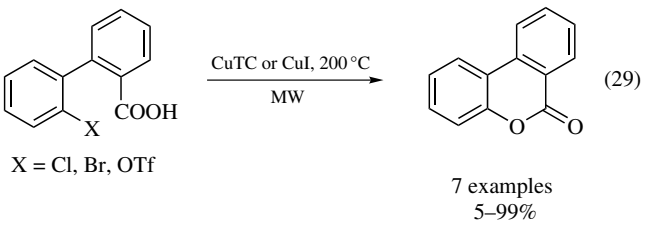
(**8**) 95.5% ee

Promoter for the Formation of C–O and C–N Bonds. *N*-Substituted imines were prepared by the copper-catalyzed N-imination of boronic acids and organostannanes with *O*-acyl ketoximes (eq 28).[32] In this process, both CuTC and $Cu(OAc)_2$ were equally effective to carry out the reaction.



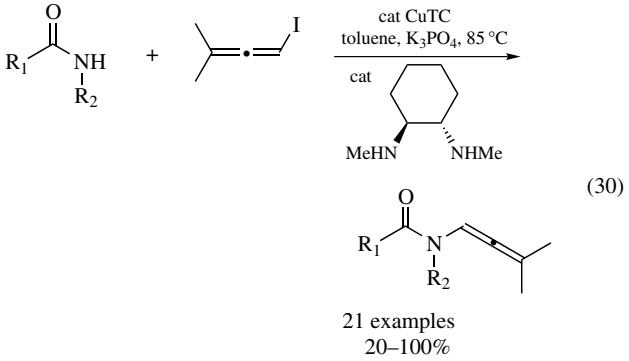
(28)

In their synthesis of benzopyranones and Isolamellarin alkaloids, Thasana et al. developed a CuTC-mediated, microwave-assisted C_{aryl}–$O_{carboxylic}$ coupling under somewhat forcing conditions (eq 29).[33]



(29)

Amides, carbamates, and ureas displayed excellent reactivity in the formation of allenamides. These substrates cross-coupled with allenyl halides in the presence of a catalytic amount of CuTC and a diamine ligand (eq 30).[34]



(30)

Related Reagents. Cu^{I} Diphenylphosphinate (CuDDP); Cu^{I} 3-methylsalicylate (CuMeSal).

1. Allred, G. D.; Liebeskind, L. S., *J. Am. Chem. Soc.* **1996**, *118*, 2748.
2. Falck, J. R.; Patel, P. K.; Bandyopadhyay, A., *J. Am. Chem. Soc*. **2007**, *129*, 790.
3. Zhang, S.; Zhang, D.; Liebeskind, L. S., *J. Org. Chem*. **1997**, *62*, 2312.
4. Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C., *Pure Appl. Chem.* **2002**, *74*, 115.
5. Liebeskind, L. S.; Srogl, J., *J. Am. Chem. Soc*. **2000**, *122*, 11260.
6. Yu, Y.; Liebeskind, L. S., *J. Org. Chem*. **2004**, *69*, 3554.
7. Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S., *Org. Lett*. **2003**, *5*, 3033.
8. Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S., *J. Am. Chem. Soc*. **2007**, *129*, 1132.
9. Yang, H.; Liebeskind, L. S., *Org. Lett*. **2007**, *9*, 2993.
10. Rodriguez-Cendejas, C. G.; Liebeskind, L. S.; Peña-Cabrera, E., *ARKIVOC* **2005**, (*vi*), 250.
11. Prokopcová, H.; Pisani, L.; Kappe, C. O., *Synlett* **2007**, 43.
12. Prokopcová, H.; Kappe, C. O., *J. Org. Chem.* **2007**, *72*, 4440.
13. Lengar, A.; Kappe, C. O., *Org. Lett*. **2004**, *6*, 771.
14. Nishihara, Y.; Inoue, Y.; Fujisawa, M.; Takagi, K., *Synlett* **2005**, 2309.
15. Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L., *Org. Lett*. **2002**, *4*, 983.
16. Aguilar-Aguilar, A.; Liebeskind, L. S.; Peña-Cabrera, E., *J. Org. Chem*. **2007**, *72*, 8539.
17. Aguilar-Aguilar, A.; Peña-Cabrera, E., *Org. Lett*. **2007**, *9*, 4163.
18. Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Newmann, L., *Org. Lett*. **2003**, *5*, 4349.
19. Savarin, C.; Srogl, J.; Liebeskind, L. S., *Org. Lett*. **2001**, *3*, 91.
20. Savarin, C.; Liebeskind, L. S., *Org. Lett*. **2001**, *3*, 2149.
21. Liebeskind, L. S.; Srogl, J., *Org. Lett*. **2002**, *4*, 979.
22. Peña-Cabrera, E.; Aguilar-Aguilar, A.; González-Domínguez, M.; Lager, E.; Zamudio-Vázquez, R.; Godoy-Vargas, J.; Villanueva-García, F., *Org. Lett*. **2007**, *9*, 3985.
23. Zhang, Z.; Liebeskind, L. S., *Org. Lett*. **2006**, *8*, 4331.
24. Borsato, G.; De Lucchi, O.; Fabris, F.; Groppo, L.; Lucchini, V.; Zambon, A., *J. Org. Chem*. **2002**, *67*, 7892.
25. Palais, M. I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vaugnoux-d'Augustin, A.; Rosset, S.; Bernardinelli, G.; Alexakis, A., *Angew. Chem., Int. Ed*. **2007**, *46*, 7462.
26. Li, K.; Alexakis, A., *Angew. Chem., Int. Ed*. **2006**, *45*, 7600.
27. d'Agustin, M.; Palais, L.; Alexakis, A., *Angew. Chem., Int. Ed*. **2005**, *44*, 1376.
28. Esquivias, J.; Gómez-Arrayás, R.; Carretero, J. C., *J. Org. Chem*. **2005**, *70*, 7451.
29. Faciola, C. A.; Tissot-Croset, K.; Alexakis, A., *Angew. Chem., Int. Ed*. **2006**, *45*, 5995.
30. Faciola, C. A.; Alexakis, A., *Angew. Chem., Int. Ed*. **2007**, *46*, 2619.
31. Carosi, L.; Hall, D. G., *Angew. Chem., Int. Ed*. **2007**, *46*, 5913.
32. Liu, S.; Yu, Y.; Liebeskind, L. S., *Org. Lett*. **2007**, *9*, 1947.
33. Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.; Ruchirawat, S. J., *Org. Chem*. **2007**, *72*, 9379.
34. Trost, B.; Stiles, D., *Org. Lett*. **2005**, *7*, 2117.

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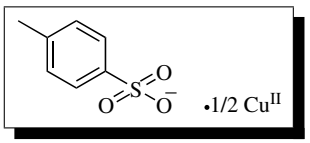
Copper(II) Toluenesulfonate



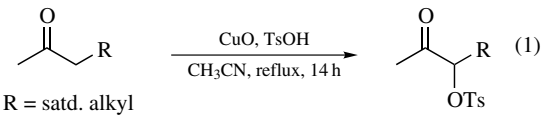
[7144-37-8] $C_{14}H_{14}S_2O_6Cu$ (MW 405.98)
InChI = 1/2C7H8O3S.Cu/c2*1-6-2-4-7(5-3-6)11(8,9)10;/h2*2-5H,1H3,(H,8,9,10);/q;;+2/p-2/f2C7H7O3S.Cu/q2*-1;m
InChIKey = MRYMYQPDGZIGDM-UZEVGVDXCZ

(reagent for regiospecific α-sulfonyloxylation of unsymmetrical ketones and a source of weakly coordinating anion in palladium-catalyzed reactions)

Physical Data: reagent decomposes at ≥ 290 °C.
Solubility: soluble in acetonitrile and many polar solvents.
Analysis of Reagent Purity: metal content determined by EDTA complexometry using a murexide indicator; anion determination using acid cation exchange resin followed by titration of eluted acid with NaOH.[1]
Preparative Methods: readily isolated as a pale-blue hexahydrate complex from aqueous reaction of either *p*-toluenesulfonic acid and copper(II) carbonate[1] or stoichiometric amounts of silver(I) *p*-toluenesulfonate and copper(II) chloride dihydrate.[2] The reagent is prepared in situ via reaction of copper oxide and *p*-toluenesulfonic acid in refluxing CH_3CN.[3]
Purity: dried at 70 °C under vacuum to give the pale-green anhydrous reagent.
Handling, Storage, and Precautions: can be stored indefinitely at room temperature under an inert atmosphere.

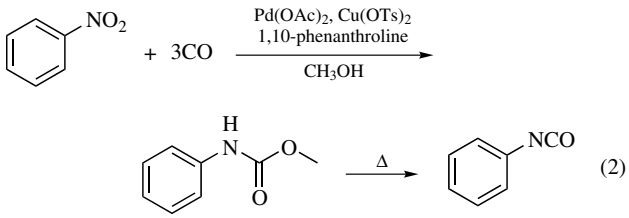
α-Sulfonyloxylation. The reagent reacts regiospecifically with various unsymmetrical 2-alkanones to give 3-tosyloxy-2-alkanones exclusively and in reasonable yields (eq 1).[3] This methodology does not require prior manipulation of the unsymmetrical ketone, such as silyl enol ether or enol acetate formation, to give a regioisomerically pure product, as is the case when using Koser's reagent[4] and related derivatives or *p*-nitrobenzenesulfonyl peroxide.[5] Reaction time can be drastically reduced using solvent-free conditions coupled with microwave irradiation.[6] The microwave assisted reaction retains the desired regioselectivity with minimal effect on the overall yield and allows for direct regioselective α-sulfonyloxylation of unsymmetrical sterically

hindered α-methine ketones, which are inaccessible using the conventional heating methodology. Products of these reactions have been shown to be useful precursors for α-amino ketones as well as α-hydroxy ketones and acetals.[7]



(1)

Anion Source for Palladium Catalysis. The reagent serves as a source of weakly coordinating anions in the palladium-catalyzed formation of mixed phenyl ureas, a known class of commercially available herbicides, using palladium(II) acetate, copper(II) toluenesulfonate, and 2,2′-dipyridyl as the catalyst system.[8] Other studies have suggested that use of this reagent to form palladium salts may have useful applications in the reductive carbonylation of nitroaromatic compounds to give isocyanates via initial carbamate formation (eq 2).[9]



(2)

Related Reagents. Copper(II) Methanesulfonate; Copper(II) Nitrobenzenesulfonate; Thallium(III) Toluenesulfonate.[10] Indirect α-Sulfonyloxylation has been achieved using Koser's reagent and related derivatives;[11] *p*-Nitrobenzenesulfonyl Peroxide; other related reagents.[12]

1. Bombin, M.; Guerrero, A.; Martinez-Zaporta, M. A.; Ramirez, A., *Thermochimica Acta* **1989**, *146*, 341.
2. Arduini, A. L.; Garnett, M.; Thompson, R. C.; Wong, T. C. T., *Can. J. Chem.* **1975**, *53*, 3812.
3. Lee, J. C.; Choi, Y., *Tetrahedron Lett.* **1998**, *39*, 3171.
4. Moriarty, R. M.; Penmasta, R.; Awasthi, A. K.; Epa, W. R., *J. Org. Chem.* **1989**, *54*, 1101.
5. Hoffman, R. V.; Carr, C. S.; Jankowski, B. C., *J. Org. Chem.* **1985**, *25*, 5148.
6. Lee, J. C.; Choi, Y., *Tetrahedron Lett.* **1999**, *40*, 8877.
7. Hoffman, R. V., *Tetrahedron* **1991**, *47*, 1109.
8. Tafesh, A. M.; Weiguny, J., *Chem. Rev.* **1996**, *96*, 2035.
9. Drent, E., *Pure Appl. Chem.* **1990**, *62(4)*, 661.
10. Khanna, M. S.; Garg, C. P.; Kapoor, R. P., *Tetrahedron Lett.* **1992**, *33*, 1495.
11. Hatzigrigoriou, E.; Varvoglis, A.; Bakola-Christianopoulou, M. J., *J. Org. Chem.* **1990**, *55*, 315.
12. Moriarty, R. M.; Vaid, R. K.; Koser, G. F., *Synlett* **1990**, *7*, 365.

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Copper(I) Trifluoromethanesulfonate

[42152-44-3] $CCuF_3O_3S$ (MW 212.62)
(2:1 benzene complex)
InChI = 1/CHF3O3S.Cu/c2-1(3,4)8(5,6)7;/h(H,5,6,7);/q;+1/p-1/fCF3O3S.Cu/q-1;m/rCCuF3O3S/c2-8-9(6,7)1(3,4)5
InChIKey = YNYHGRUPNQLZHB-SQWZUGTLCP
[37234-97-2] $C_8H_6Cu_2F_6O_6S_2$ (MW 503.34)
InChI = 1/C6H6.2CHF3O3S.2Cu/c1-2-4-6-5-3-1;2*2-1(3,4)8(5,6)7;;/h1-6H;2*(H,5,6,7);;
InChIKey = GNXZWVVAAMVOJY-UJWRWXPACK
[42152-46-5]
InChI = 1/C6H6.2CHF3O3S.2Cu/c1-2-4-6-5-3-1;2*2-1(3,4)8(5,6)7;;/h1-6H;2*(H,5,6,7);;
InChIKey = GNXZWVVAAMVOJY-UJWRWXPACK

(efficient catalyst for $2\pi + 2\pi$ photocycloadditions and other photoreactions of alkenes,[1] for decomposition of diazo compounds into carbenoids suited for, eventually asymmetric, cyclopropanation of alkenes, X-H insertion or ylide formation, for aziridination of olefins, conjugate addition to α,β-enones, allylic alkylation or oxidation, addition to imines and C-X coupling; also a selenophilic and thiophilic Lewis acid that enhances the nucleofugacity of selenide and sulfide leaving groups)

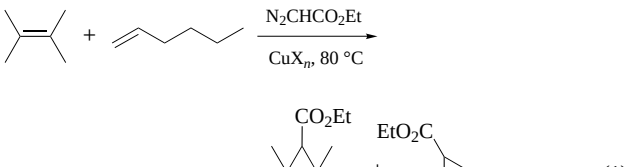
Alternate Name: copper(I) triflate.
Physical Data: moisture-sensitive white crystalline solid.
Solubility: soluble in MeCN, AcOH, 2-butanone, alkenes; slightly soluble in benzene.
Form Supplied in: commercially available or can be prepared. Better results are often obtained when freshly prepared $(CuOTf)_2$-C_6H_6 complex is used.
Preparative Methods: copper(I) trifluoromethanesulfonate (CuOTf) was first prepared as a solution in acetonitrile by synproportionation of copper(II) trifluoromethanesulfonate with copper(0).[2] The Cu(I) in these solutions is strongly coordinated with acetonitrile, forming complexes analogous to tetrakis(acetonitrile) copper(I) perchlorate.[3] A white crystalline solid benzene complex, $(CuOTf)_2 \cdot C_6H_6$, is prepared by reaction of a suspension of copper(I) oxide in benzene with trifluoromethanesulfonic anhydride.[4] Traces of trifluoromethanesulfonic acid apparently catalyze the reaction.[5] CuOTf is generated in situ by the reduction of $Cu(OTf)_2$ with diazo compounds, substituted hydrazines or dialkylzinc.
Handling, Storage, and Precautions: moisture sensitive. Should be kept under argon and handled under an inert atmosphere.

Original Commentary

Robert G. Salomon
Case Western Reserve University, Cleveland, OH, USA

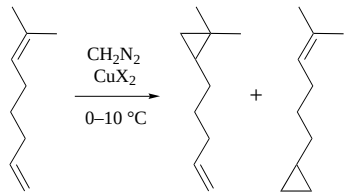
Cyclopropanation with Diazo Compounds. Copper(I) triflate is a highly active catalyst for the cyclopropanation of alkenes with diazo compounds.[6] In contrast to other more extensively ligated copper catalysts, e.g. copper(II) acetylacetonate, that favor cyclopropanation of the most highly substituted C=C bond,

cyclopropanations catalyzed by CuOTf show a unique selectivity for cyclopropanation of the least alkylated C=C bond in both intermolecular (eq 1) and intramolecular (eq 2) competitions. The same selectivity is found with $Cu(OTf)_2$ as *nominal* catalyst. This is because $Cu(OTf)_2$ is reduced by the diazo compound to CuOTf, and CuOTf is the *actual* cyclopropanation catalyst in both cases.[6] Selective cyclopropanation of the least substituted C=C bond is a consequence of the alkene coordinating with the catalyst prior to interaction with the diazo compound, and the increase in stability of Cu^I–alkene complexes with decreasing alkyl substitution on the C=C bond. For catalysts with more strongly ligated Cu^I, an electrophilic carbene or carbenoid intermediate reacts with the free alkene, and the preference for cyclopropanation of the more highly substituted C=C bond arises from the enhancement of alkene nucleophilicity with increasing alkyl substitution.



(1)

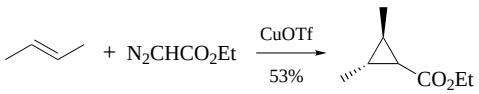
CuX_n		Ratio	
CuOTf	17%	0.25:1	67%
$Cu(OTf)_2$	21%	0.27:1	77%
$Cu(acac)_2$	61%	1.78:1	35%



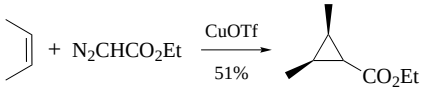
(2)

X = acetylacetonate	86%	14%
X = triflate	33%	66%

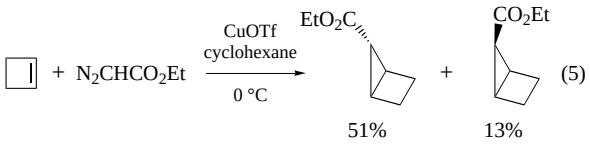
Cyclopropanecarboxylic esters are conveniently available, even from volatile alkenes, because CuOTf promotes cyclopropanations in good yields at low temperatures. Thus *trans*- and *cis*-2-butenes, boiling under reflux, react stereospecifically with ethyl diazoacetate to produce the corresponding ethyl 2,3-dimethylcyclopropanecarboxylates (eq 3 and eq 4),[6] and cyclobutene reacts with ethyl diazoacetate at 0 °C to deliver a mixture of *exo*- and *endo*-5-ethoxycarbonylbicyclo[2.1.0]pentanes (eq 5).[7]



(3)

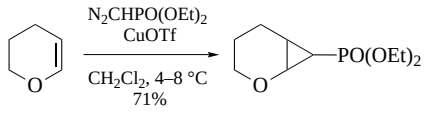


(4)

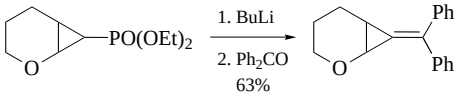


(5)

CuOTf is an outstandingly effective catalyst for the synthesis of cyclopropyl phosphonates by the reaction of diethyl diazomethylphosphonate with alkenes (eq 6).[8] The resulting cyclopropylphosphonates are useful intermediates for the synthesis of alkylidenecyclopropanes by Wadsworth–Emmons alkenation with aromatic carbonyl compounds (eq 7).[8]

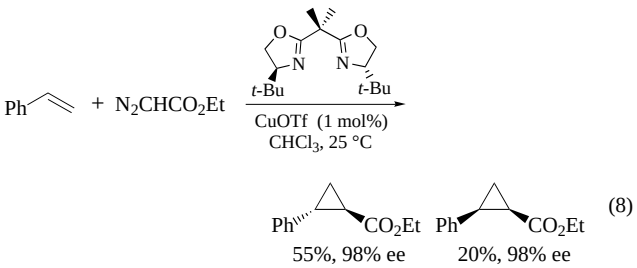


(6)

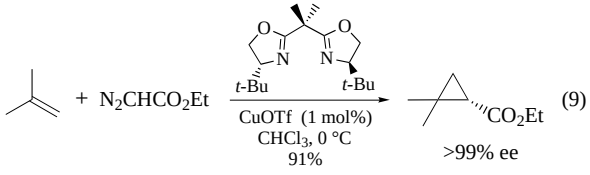


(7)

A complex of a chiral, nonracemic bis(oxazoline) with CuOTf is a highly effective catalyst for asymmetric cyclopropanation of alkenes.[9] Copper(II) triflate complexes do not catalyze the reaction unless they are first converted to Cu^I by reduction with a diazo compound or with phenylhydrazine. CuOTf complexes are uniquely effective. Thus the observed enantioselectivity and catalytic activity, if any, are much lower with other Cu^I or Cu^{II} salts including halide, cyanide, acetate, and even perchlorate. Both enantiomers of the bis(oxazoline) ligand are readily available. Spectacularly high levels of asymmetric induction are achieved with both mono- (eq 8) and 1,1-disubstituted alkenes (eq 9).

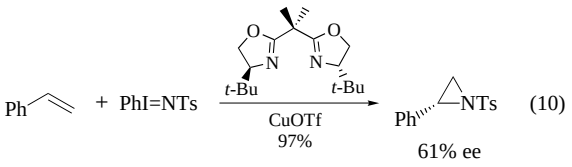


(8)



(9)

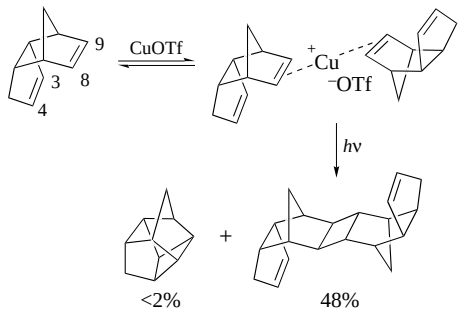
Asymmetric Aziridination. A chiral, nonracemic bis(oxazoline) complex of copper(I) triflate catalyzes asymmetric aziridination of styrene in good yield (eq 10).[9] However, enantioselectivity is not as high as the corresponding cyclopropanation (eq 8).



(10)

Photocycloadditions. CuOTf is an exceptionally effective catalyst for $2\pi + 2\pi$ photocycloadditions of alkenes.[1] Thus while CuBr promotes photodimerization of norbornene in only 38% yield,[10] the same reaction affords dimer in 88% yield with CuOTf as catalyst (eq 11).[11] A mechanistic study of this reaction revealed that although both 1:1 and 2:1 alkene Cu^{I} complexes are in equilibrium with free alkene and both the 1:1 and 2:1 complexes absorb UV light, only light absorbed by the 2:1 complex results in photodimerization. In other words, photodimerization requires precoordination of both C=C bonds with the Cu^{I} catalyst. Thus the exceptional ability of CuOTf, with its weakly coordinating triflate counter anion, to form π-complexes with as many as four C=C bonds[12] is of paramount importance for its effectiveness as a photodimerization catalyst.

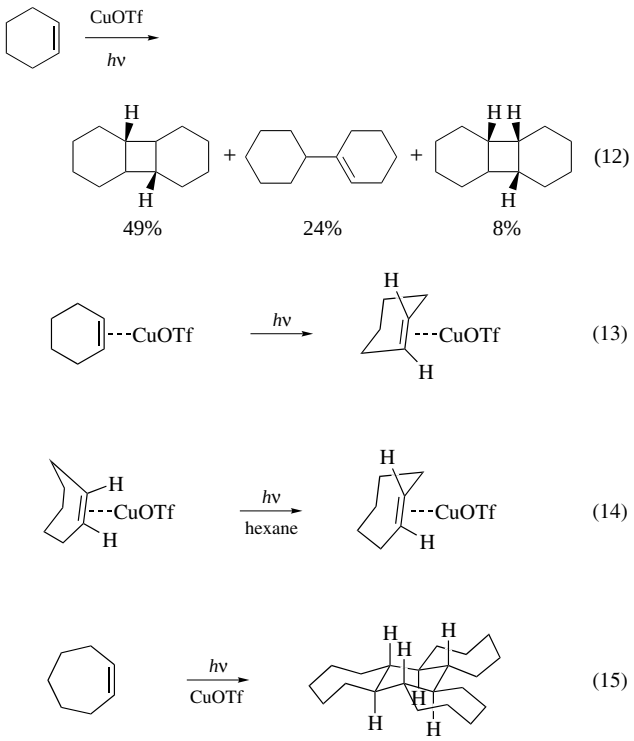
The importance of precoordination is also evident in the CuOTf-promoted $2\pi + 2\pi$ photocycloaddition of *endo*-dicyclopentadiene. This diene forms an isolable 2:1 complex with CuOTf involving *exo*-monodentate coordination with the 8,9-C=C bond of two molecules of diene. Consequently, intermolecular $2\pi + 2\pi$ photocycloaddition involving *exo* addition to the 8,9-C=C bond is strongly favored over intramolecular reaction between the 8,9- and 3,4-C=C bonds (eq 11).[11] This contrasts with the intramolecular photocycloaddition that is promoted by high energy triplet sensitizers.[12]



(11)

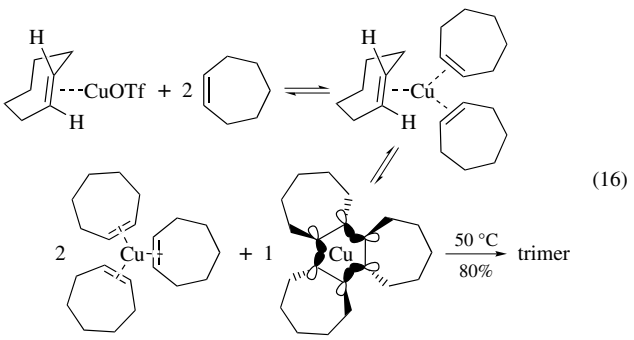
Especially interesting is the *trans,anti,trans* stereochemistry of the major cyclobutane product generated in the photodimerization of cyclohexene (eq 12).[13] It was noted that the formation of this product may be the result of a preliminary CuOTf promoted *cis–trans* photoisomerization that generates a *trans*-cyclohexene intermediate (eq 13).[13] Since one face of the *trans* C=C bond is shielded by a polymethylene chain, the *trans*-cyclohexene is restricted to suprafacial additions. Although a highly strained *trans*-cyclohexene intermediate could be stabilized by coordination with Cu^{I}, such a complex has not been isolated.

An isolable CuOTf complex of a highly strained alkene, *trans*-cycloheptene, is produced by UV irradiation of a hexane solution of *cis*-cycloheptene in the presence of CuOTf (eq 14).[14] Photocycloaddition of cycloheptene is also catalyzed by CuOTf. Surprisingly, the major product is not a *trans,anti,trans* dimer analogous to that formed from cyclohexene (eq 12) but rather a *trans,anti,trans,anti,trans* trimer (eq 15).[15]



(12)
(13)
(14)
(15)

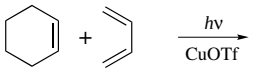
Dissolution of the *trans*-cycloheptene–CuOTf complex in cycloheptene and evaporation of the solvent delivers a tris alkene complex of CuOTf containing one *trans*-cycloheptene and two *cis*-cycloheptene ligands. Heating *trans*-cycloheptene–CuOTf in neat *cis*-cycloheptene delivers the *trans,anti,trans,anti,trans* trimer (eq 16). Experiments with *cis*-cycloheptene-d_4 show that the cyclotrimerization involves only *trans*-cycloheptene molecules, although the reaction is accelerated by the presence of *cis*-cycloheptene.[16] A likely explanation for these observations is 'concerted "template" cyclotrimerization' of a tris-*trans*-cycloheptene–CuOTf complex formed by ligand redistribution (eq 16).[16]

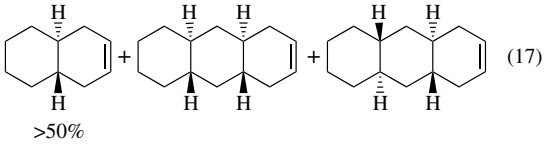


(16)

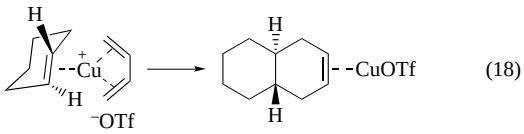
The involvement of a transient photogenerated *trans*-cyclohexene–CuOTf intermediate was also adduced to explain CuOTf catalysis of photoinduced $2\pi + 4\pi$ cycloaddition between *cis*-cyclohexene and 1,3-butadiene (eq 17).[17] In contrast to thermal Diels–Alder reactions, this reaction generates *trans*-Δ^2-octalin rather than the *cis* cycloadduct expected for a $2\pi_s + 4\pi_s$ cycloaddition. A mechanism was proposed that involves the $2\pi_s + 4\pi_s$ cycloaddition of a *trans*-cyclohexene with 1,3-butadiene in the coordination sphere of Cu^{I} (eq 18).[17]

That CuOTf-catalyzed $2\pi + 2\pi$ photocycloadditions are not restricted to cyclic alkenes was first demonstrated in mixed cycloadditions involving allyl alcohol. To suppress homodimerization of *endo*-dicyclopentadiene (i.e. eq 11) the diene to Cu^{I} ratio is maintained at < 1:1 and allyl alcohol is used as solvent. Under these conditions, a high yield of mixed cycloadduct is generated (eq 19).[18]

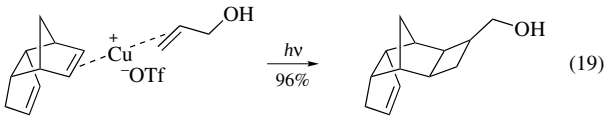




(17)

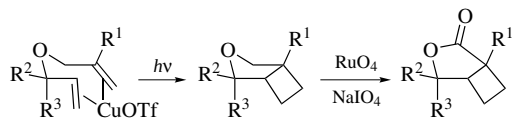


(18)



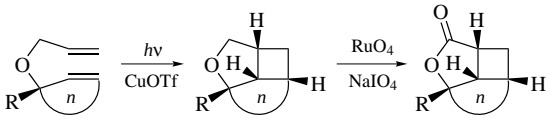
(19)

That both C=C bonds participating in $2\pi + 2\pi$ photocycloadditions can be acyclic is evident from the photobicyclization reactions of simple diallyl ethers that deliver bicyclic tetrahydrofurans (eq 20).[19,20] In conjunction with ruthenium(IV) oxide-catalyzed oxidation by sodium periodate, these CuOTf-catalyzed photobicyclizations provide a synthetic route to butyrolactones from diallyl ethers (eq 20).[20] The synthetic method is applicable to the construction of multicyclic tetrahydrofurans and butyrolactones from diallyl ethers (eq 21 and eq 22) as well as from homoallyl vinyl ethers (eq 23).[20]



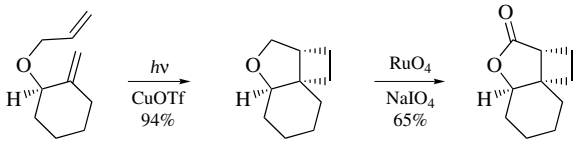
(20)

R^1	R^2	R^3	Yield (%)	Yield (%)
H	H	H	52	91
Me	Me	H	56	94
Me	Me	Me	54	44
Me	H	H	54	56
n-Bu	H	Me	83	83



(21)

R	*n*	Yield (%)	Yield (%)
H	5	47	73
H	8	56	56
Me	5	28	87
Me	6	35	82



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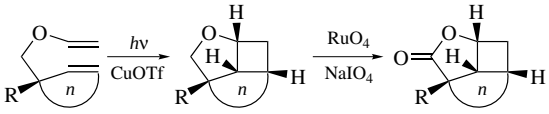
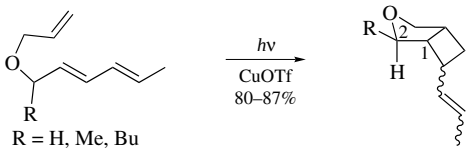


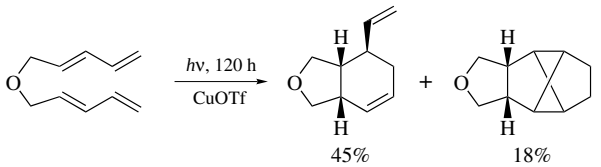
(23)

R	*n*	Yield (%)	Yield (%)
H	5	92	78
Me	5	50	71
H	6	48	85

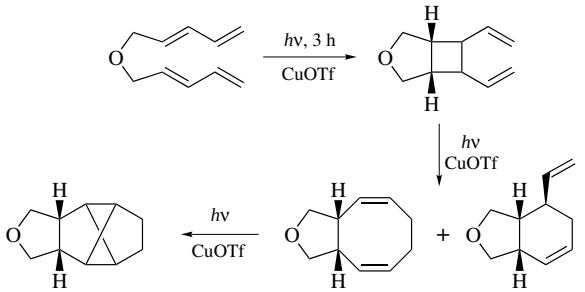
3-Oxabicyclo[3.2.0]heptanes are also produced in the CuOTf-catalyzed photocycloadditions of allyl 2,4-hexadienyl ethers (eq 24).[21] The CuOTf-catalyzed photocycloadditions of bis-2,4-hexadienyl ethers are more complex. Thus UV irradiation of 5,5′-oxybis[(*E*)-1,3-pentadiene] in THF for 120 h produces vinylcyclohexene and tricyclo[3.3.0.$0^{2,6}$]octane derivatives (eq 25).[22] However, shorter irradiations reveal that these products arise by secondary CuOTf-catalyzed rearrangements of 6,7-divinyl-3-oxabicyclo[3.2.0]heptanes that are the primary photoproducts (eq 26). UV irradiation of the divinylcyclobutane intermediates in the presence of CuOTf promotes formal [1,3]- and [3,3]-sigmatropic rearrangements to produce a vinylcyclohexene and a 1,5-cyclooctadiene that is the immediate precursor of the tricyclo[3.3.0.$0^{2,6}$]octane.



(24)



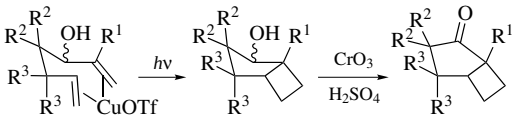
(25)



(26)

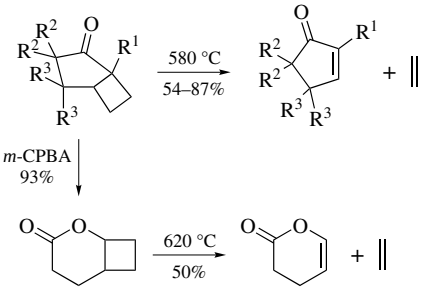
CuOTf-catalyzed photobicyclization of 1,6-heptadien-3-ols produces bicyclo[3.2.0]heptan-2-ols (eq 27).[23] In conjunction with pyrolytic fragmentation of the derived ketones, these CuOTf-catalyzed photobicyclizations provide a synthetic route to 2-cyclopenten-1-ones from 1,6-heptadien-3-ols (eq 28).[23] The derived

ketones can also be converted into lactones by Baeyer–Villiger oxidation and, in conjunction with pyrolytic fragmentation, CuOTf-catalyzed photobicyclizations provide a synthetic route to enol lactones of glutaraldehydic acid from 1,6-heptadien-3-ols (eq 28).[23]



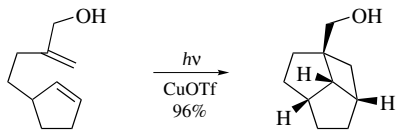
(27)

R^1	R^2	R^3	Yield (%)	Yield (%)
H	H	H	86	78
Me	H	H	81	67
H	Me	H	91	92
H	H	Me	84	92
Me	Me	H	83	93

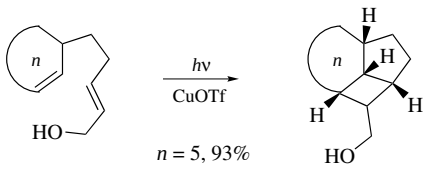


(28)

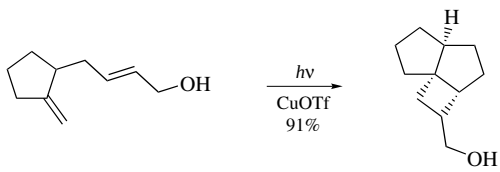
Copper(I) triflate-catalyzed photobicyclization of β- and γ-(4-pentenyl)allyl alcohols provides a synthetic route to various multicyclic carbon networks in excellent yields (eq 29–31).[24] The reaction was exploited in a total synthesis of the panasinsene sesquiterpenes (eq 32).[25] It is especially noteworthy in this regard that attempted synthesis of a key tricyclic ketone intermediate for the panasinsenes by the well-known photocycloaddition of isobutene to an enone failed to provide any of the requisite cyclobutyl ketone (eq 33).[25]



(29)

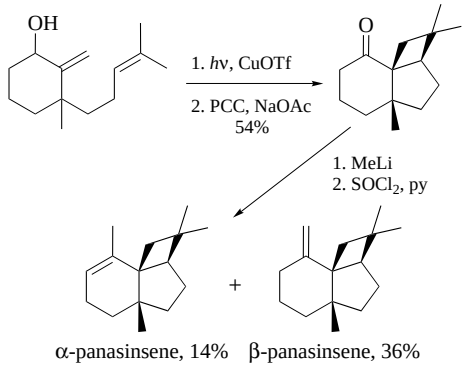


(30)

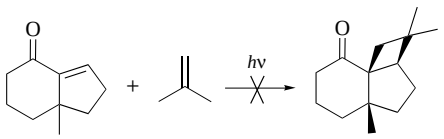


(31)

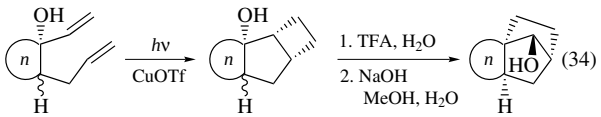
In conjunction with carbocationic skeletal rearrangement, photobicyclization of 1,6-heptadien-3-ols provides a synthetic route to 7-hydroxynorbornanes (eq 34).[26] Noteworthy is the stereoselective generation of *exo*-1,2-polymethylenenorbornanes from either the *exo* or *endo* epimer of 2,3-polymethylenebicyclo[3.2.0] heptan-3-ol.



(32)



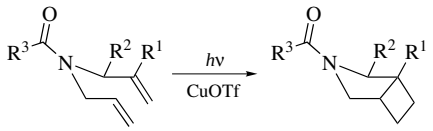
(33)



(34)

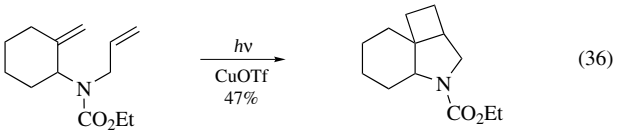
n	Yield (%)	Yield (%)
5	70–75	64–85
6	51–84	76–77
7	73	73
8	74	66

N,N-Diallylamides are recovered unchanged when irradiated in the presence of CuOTf.[27] This is because the amide chromophore interferes with photoactivation of the Cu^I–alkene complex. Thus CuOTf–alkene complexes containing one, two, three, or even four coordinated C=C bonds exhibit UV absorption at 235 ± 5 nm (ε_{max} 2950 ± 450).[12] The CuOTf complex of ethyl *N,N*-diallylcarbamate exhibits λ_{max} = 233.4 nm (ε_{max} 2676) but the free ligand is virtually transparent at this wavelength. Consequently, UV irradiation of ethyl *N,N*-diallylcarbamates in the presence of CuOTf delivers bicyclic (eq 35) or tricyclic (eq 36) pyrrolidines incorporating the 3-azabicyclo[3.2.0]heptane ring system.[27]



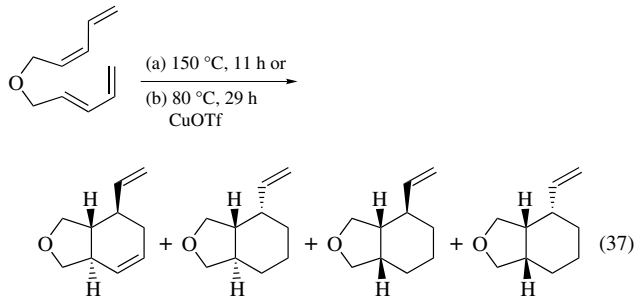
(35)

R^1	R^2	R^3	$\varepsilon_{233\ nm}$	Yield (%)
H	H	Me	192	0
H	H	H	231	0
H	H	OEt	15	74
H	Me	OEt	–	60
Me	H	OEt	–	76



(36)

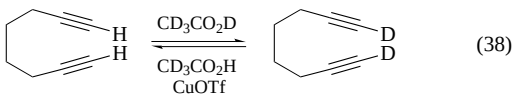
Catalyzed Diels–Alder Reactions. The uncatalyzed thermal intramolecular Diels–Alder reaction of 5,5′-oxybis[(*E*)-1,3-pentadiene] nonstereoselectively generates four isomeric 4-vinylcyclohexenes (eq 37). The major product has a *trans* ring fusion, in contrast to the single *cis* ring-fused isomer generated in the copper(I) triflate-catalyzed photoreaction of the same tetraene (eq 25). Copper(I) triflate also catalyzes a thermal Diels–Alder reaction of 5,5′-oxybis[(*E*)-1,3-pentadiene] that proceeds under milder conditions than the uncatalyzed reaction. The stereoselectivity is remarkably enhanced, generating mainly the major isomer of the uncatalyzed thermal reaction and a single *cis*-fused isomer (eq 37) that is different than the one favored in the photochemical reaction (eq 25).



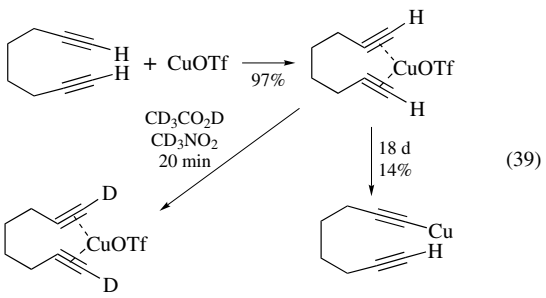
(37)

(a)	46%	10%	21%	3%
(b)	76%	<1%	<1%	11%

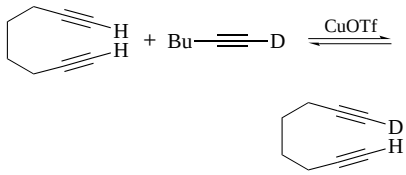
C_{sp}–H Bond Activation. Hydrogen–deuterium exchange between terminal alkynes and CD_3CO_2D is catalyzed by CuOTf (eq 38).[28] Proton NMR studies revealed that CuOTf and alkynes form π-complexes that rapidly exchange coordinated with free alkyne. A complex of CuOTf with 1,7-octadiene was isolated (eq 39). The complex rapidly exchanges terminal alkynic hydrogen with deuterium from CD_3CO_2D and undergoes a much slower conversion to a copper alkynide (eq 39).[28] Exchange of alkynic hydrogen and deuterium is also catalyzed by CuOTf (eq 40).[28]



(38)

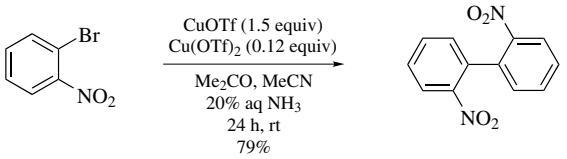


(39)



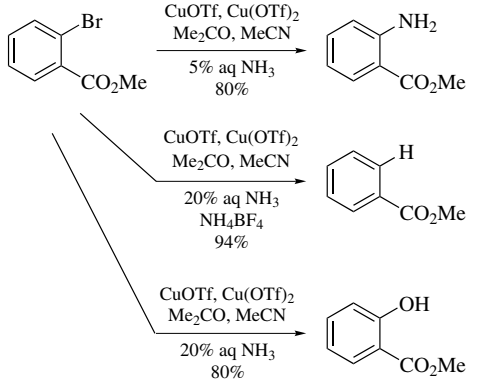
(40)

Activation of Aryl Halides. Ullmann coupling of *o*-bromonitrobenzene is accomplished under exceptionally mild conditions and in homogeneous solution by reaction with copper(I) triflate in the presence of aqueous NH_3 (eq 41).[29] Yields are enhanced by the presence of a small quantity of copper(II) triflate. That the reaction is diverted to reductive dehalogenation by ammonium tetrafluoroborate is presumptive evidence for an organocopper intermediate that can be captured by protonation.



(41)

Biaryl is only a minor product from the reaction of methyl *o*-bromobenzoate with CuOTf (eq 42). The major product can result from replacement of the halide by NH_2, H, or, OH.; depending on reaction conditions. In the presence of 5% aqueous NH_3, methyl anthranilate is the major product.[30] More concentrated aqueous NH_3 (20%) favors the generation of methyl salicylate, and the yield of this product is enhanced by the presence of a substantial quantity of Cu^{II} ion.[29] Reductive dehalogenation is favored by the presence of ammonium ions, presumably owing to protonolysis of an arylcopper(III) intermediate.[29]

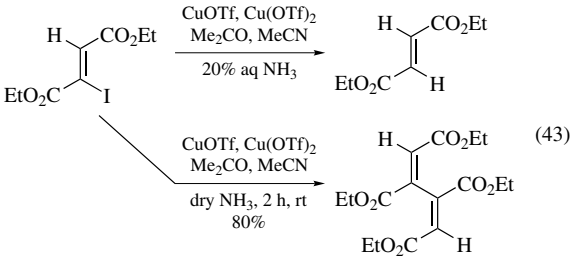


(42)

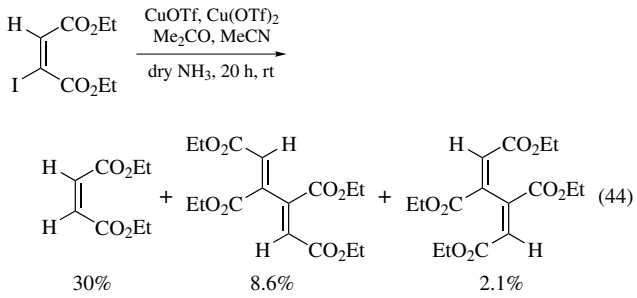
Activation of Vinyl Halides. Under the optimum conditions for reductive coupling of *o*-bromonitrobenzene (eq 41), diethyl iodofumarate gives very little coupling product; the overwhelming product was diethyl fumarate generated by hydrodehalogenation (eq 43).[29] Reductive coupling delivers *trans,trans*-1,2,3,4-tetraethoxycarbonyl-1,3-butadiene in 95% yield (GLC, or 80% of pure crystalline product) in 2 h if aqueous NH_3 is replaced by anhydrous NH_3.[29] Under the same conditions, diethyl iodomaleate undergoes 45% conversion in 20 h to deliver diethyl maleate, as well as minor amounts of *cis,cis*- and *trans,trans*-tetraethoxycarbonyl-1,3-butadiene (eq 44).[29] The stereospecificity of the reductive

dehalogenations in eq 43 and eq 44 is presumptive evidence for the noninvolvement of radicals in these reactions.

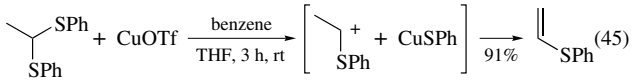
Elimination of Thiophenol from Thioacetals. Conversion of thioacetals to vinyl sulfides is accomplished under exceptionally mild conditions by treatment with $(CuOTf)_2 \cdot C_6H_6$ (eq 45).[31] The reaction involves an α-phenylthio carbocation intermediate. Three factors contribute to the effectiveness of this synthetic method: the Lewis acidity of a copper(I) cation that is unencumbered by a strongly coordinated counter anion, the solubility of the copper(I) triflate–benzene complex, and the insolubility of CuSPh in the reaction mixture. An analogous elimination reaction provides an effective route to phenylthio enol ethers from ketones (eq 46).[31]



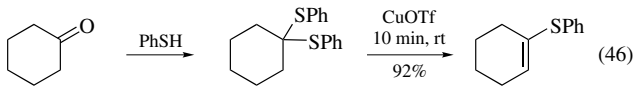
(43)



(44)

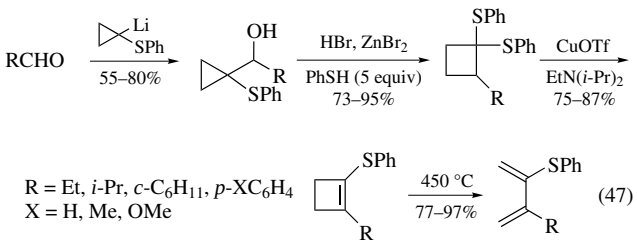


(45)



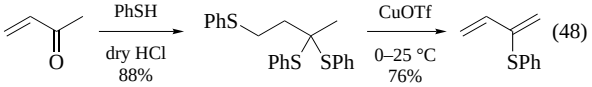
(46)

This conversion of thioacetals into vinyl sulfides was applied to a C–C connective synthesis of 2-phenylthio-1,3-butadienes from aldehydes (eq 47).[32] The key elimination step converts cyclobutanone thioacetal intermediates into 1-phenylthiocyclobutenes that undergo electrocyclic ring opening to deliver dienes.



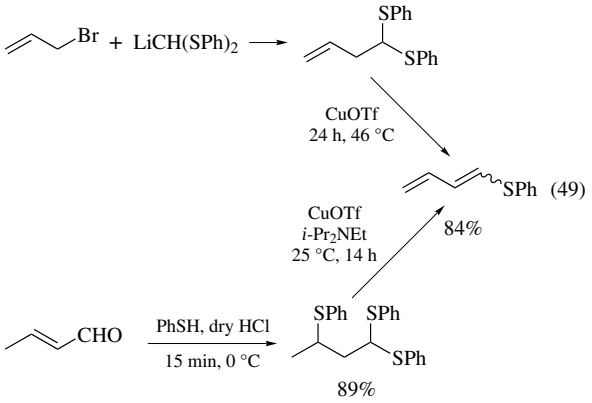
(47)

A different synthesis generates 2-phenylthio-1,3-butadienes directly by elimination of two molecules of thiophenol from β-phenylthio thioacetals that are readily available from the corresponding α,β-unsaturated ketones (eq 48).[33]

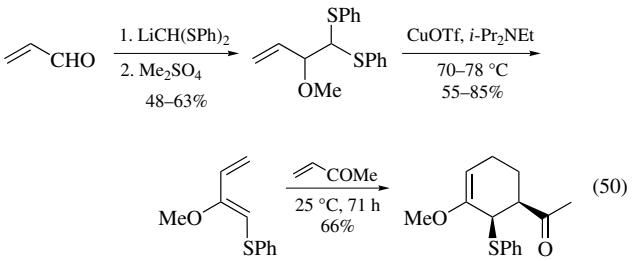


(48)

CuOTf-promoted elimination of thiophenol was exploited in two syntheses of 1-phenylthio-1,3-butadiene, one a C–C connective route from allyl bromide[31] and bis(phenylthio)-methyllithium,[34] and another from crotonaldehyde (eq 49).[33] A topologically analogous C–C connective strategy provides 2-methoxy-1-phenylthio-1,3-butadiene from acrolein (eq 50).[5,33] That the phenylthio rather than the methoxy substituent in 2-methoxy-1-phenylthio-1,3-butadiene controls the orientation of its Diels–Alder cycloadditions is noteworthy (eq 50).

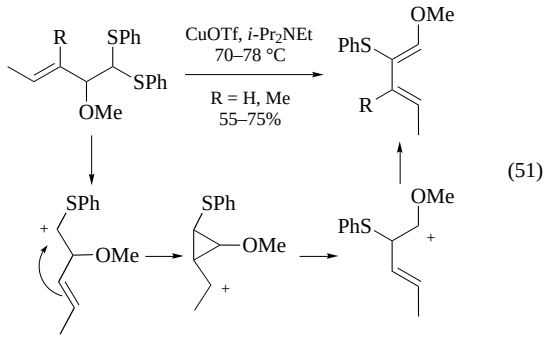


(49)



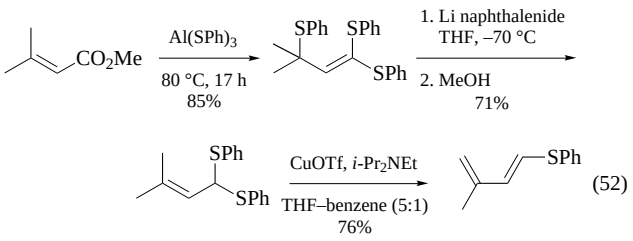
(50)

A synthesis of 4-alkyl-2-methoxy-1-phenylthio-1,3-butadienes by a simple β-elimination of thiophenol from a thioacetal is not possible owing to skeletal rearrangement that is fostered by stabilization of a cyclopropylcarbinyl carbocation intermediate by the alkyl substituent (eq 51).[35] Interconversion of an initial α-phenylthio carbocation to a more stable α-methoxy carbocation intermediate leads to the generation of a 4-alkyl-1-methoxy-2-phenylthio-1,3-butadiene instead.

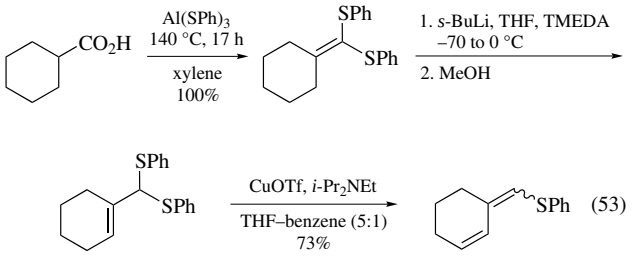


(51)

Syntheses of 1-phenylthio-1,3-butadienes from carboxylic esters (eq 52) and carboxylic acids (eq 53) are achieved by CuOTf-promoted elimination of thiophenol from intermediate thioacetals.[36]

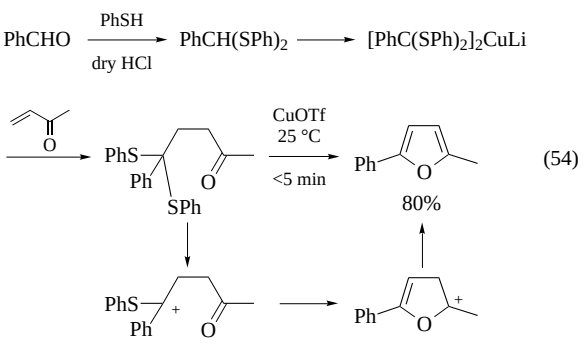


(52)



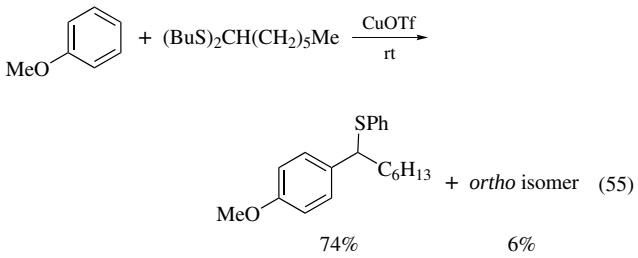
(53)

Heterocyclization of γ-Keto Dithioacetals. A C–C connective synthesis of furans is completed by a CuOTf-promoted heterocyclization of γ-keto thioacetals (eq 54).[31] Rather than simple β-elimination to generate a vinyl sulfide (eq 46), a presumed γ-keto carbocation intermediate is captured intramolecularly by an intimately juxtaposed carbonyl oxygen nucleophile.



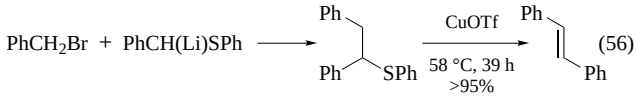
(54)

Friedel–Crafts Alkylation of Arenes with Thioacetals. $(CuOTf)_2 \cdot C_6H_6$ promotes α-thioalkylation of anisole by a dithioacetal under mild conditions (eq 55).[37]



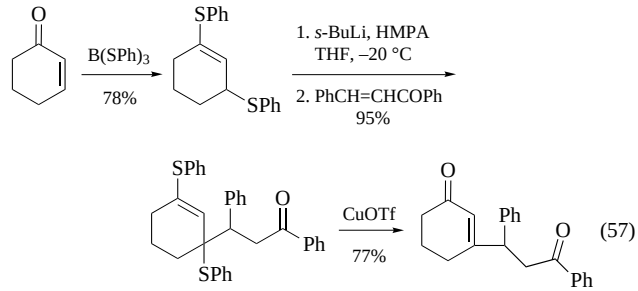
(55)

Elimination of Benzylic Phenyl Thioethers. That C–S bond activation by CuOTf is not limited to substrates that can generate sulfur-stabilized carbocation intermediates is illustrated by a C–C connective synthesis of *trans*-stilbene (eq 56).[31] The elimination of thiophenol under mild conditions is favored by benzylic stabilization of a carbocation intermediate or an E2 transition state with substantial carbocationic character.



(56)

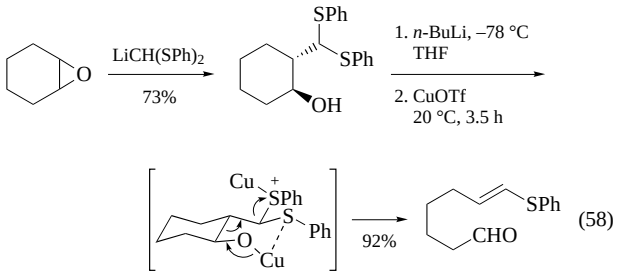
Hydrolysis of Vinylogous Thioacetals. Carbanions prepared by lithiation of γ-phenylthioallyl phenyl thioethers can serve as synthetic equivalents of β-acyl vinyl anions.[38] Umpölung of the usual electrophilic reactivity of 2-cyclohexenone is achieved by a sequence exploiting electrophilic capture of a lithiated vinylogous thioacetal and subsequent CuOTf-assisted hydrolysis (eq 57).[39] Otherwise unfunctionalized vinylogous thioacetals can be hydrolyzed to enones by mercury(II) chloride in wet acetonitrile.[38] However, the keto-substituted derivative in eq 57 gave only a 25% yield of enone by this method. A superior yield was obtained by CuOTf-assisted hydrolysis.[39]



(57)

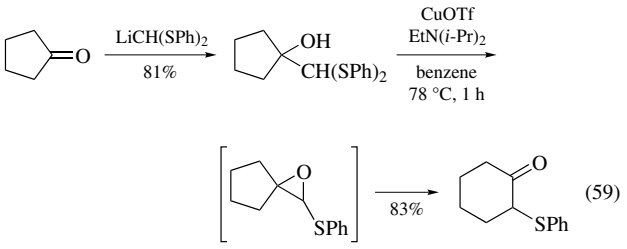
Grob Fragmentation of β-[Bis(phenylthio)methyl]-alkoxides. A method for achieving Grob-type fragmentation of five- and six-membered rings depends upon the ability of a thiophenyl group to both stabilize a carbanion and serve as an anionic leaving group. For example, reaction of cyclohexene oxide with lithium bis(phenylthio)methide[34] produces a β-[bis(phenylthio)methyl] alkanol that undergoes fragmentation in excellent yield upon treatment with butyllithium followed by CuOTf (eq 58).[40] Copper(I) trifluoroacetate is equally

effective but salts of other thiophilic metals, e.g. mercury or silver, were ineffective. Treatment of the intermediate β-[bis(phenylthio)methyl]alkanol with CuOTf in the absence of added strong base leads primarily to elimination of thiophenol as expected (see eq 45). Fragmentation does not occur with only one equivalent of CuOTf. This suggests a key intermediate with at least one Cu^{I} ion to coordinate with the alkoxide and another to activate the phenylthio leaving group (eq 58).



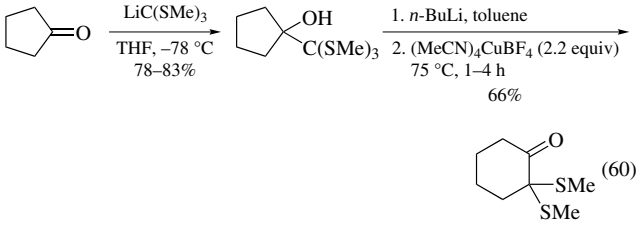
(58)

Ring-Expanding Rearrangements of α-[Bis(phenylthio) methyl]alkanols. A one-carbon ring-expanding synthesis of α-phenylsulfenyl ketones from homologous ketones depends upon the ability of a thiophenyl group to both stabilize a carbanion and serve as an anionic leaving group. For example, reaction of cyclopentanone with lithium bis(phenylthio)methide[34] produces an α-[bis(phenylthio)methyl]alkanol that rearranges to a ring-expanded α-phenylsulfenyl ketone in good yield upon treatment with CuOTf in the presence of diisopropylethylamine (eq 59).[41] Epoxy thioether intermediates are generated from the α-[bis(phenylthio)methyl]alkanols by intramolecular nucleophilic displacement of thiophenoxide.

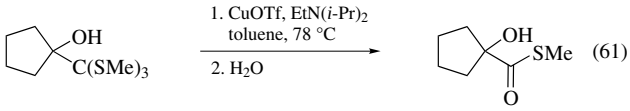


(59)

An analogous synthesis of α,α-bis(methylsulfenyl) ketones from homologous ketones by one-carbon ring expansion depends on copper(I)-promoted rearrangement of an α-tris(methylthio) methyl alkoxide intermediate (eq 60). Both tetrakis(acetonitrile) copper(I) perchlorate[42] and tetrakis(acetonitrile)copper(I) tetrafluoroborate[43] are effective in promoting the rearrangement but $(CuOTf)_2{\cdot}C_6H_6$, $HgCl_2$, or $Hg(TFA)_2$ are not. Apparently, the MeCN ligand is crucial. Furthermore, treatment of the intermediate α-[tris(methylthio)methyl] alcohol with CuOTf and EtN(*i*-Pr)$_2$ in toluene followed by aqueous workup delivers an α-hydroxy methylthio ester (eq 61),[43] in contrast to the ring-expanding rearrangement of the analogous α-[bis(phenylthio)methyl]alkanol (eq 59).[41]

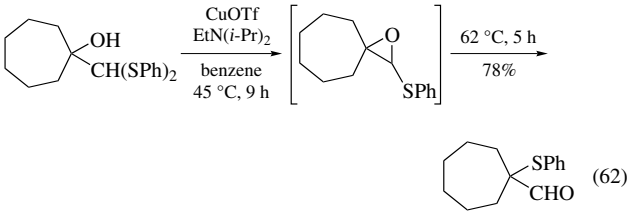


(60)



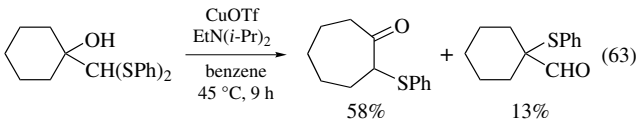
(61)

The α-[bis(phenylthio)methyl]alkanol derived from cycloheptanone does not undergo ring expansion upon treatment with CuOTf and EtN(*i*-Pr)$_2$ in benzene. Instead, 1,3-elimination of thiophenol delivers an epoxy thioether intermediate that undergoes a rearrangement involving 1,2-shift of a phenylsulfenyl group to produce an α-phenylsulfenyl aldehyde (eq 62).[41]

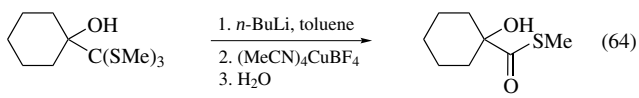


(62)

The α-[bis(phenylthio)methyl]alkanol derived from cyclohexanone, upon treatment with CuOTf and EtN(*i*-Pr)$_2$ in benzene, undergoes both ring-expanding rearrangement to deliver α-phenylsulfenylcycloheptanone as the major product, as well as rearrangement involving 1,2-shift of a phenylsulfenyl group to produce an α-phenylsulfenylcyclohexanecarbaldehyde (eq 63).[41] In contrast, neither ring expansion nor 1,2-shift of a methylsulfenyl group occurs upon treatment of α-[tris(methylthio)methyl]cyclohexanol with *n*-butyllithium followed by $(MeCN)_4CuBF_4$. Rather, after aqueous workup, an α-hydroxy methylthio ester is obtained (eq 64).[43]



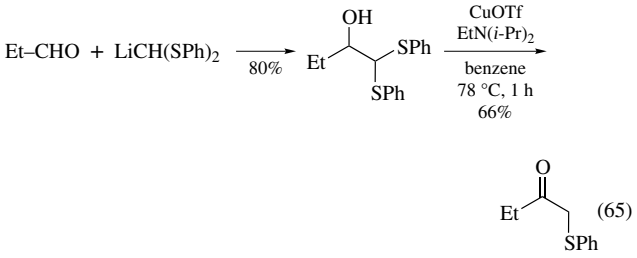
(63)



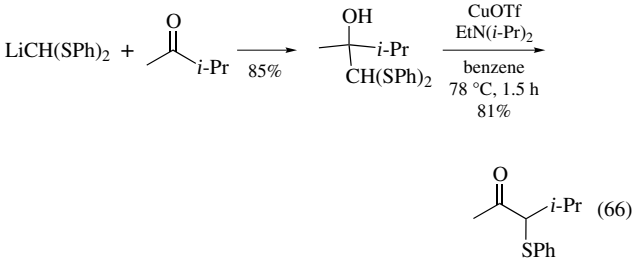
(64)

Chain-Extending Syntheses of α-Phenylsulfenyl Ketones. A C–C connective, chain-extending synthesis of α-phenylsulfenyl ketones from aldehydes (eq 65) or acyclic ketones (eq 66)[41] can be accomplished by a CuOTf-promoted activation of the α-[bis(phenylthio)methyl]alkanols generated by addition of lithium bis(phenylthio)methide.[34] Preferential migration of hydride generates phenylsulfenylmethyl ketones

from aldehydes (eq 65). Regioselective insertion of a phenylsulfenylmethylene unit occurs owing to a preference for migration of the more highly substituted alkyl group of dialkyl ketones (eq 66).

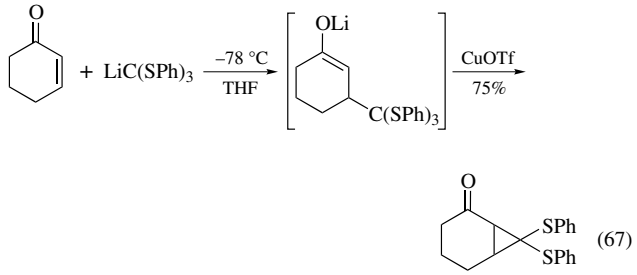


(65)



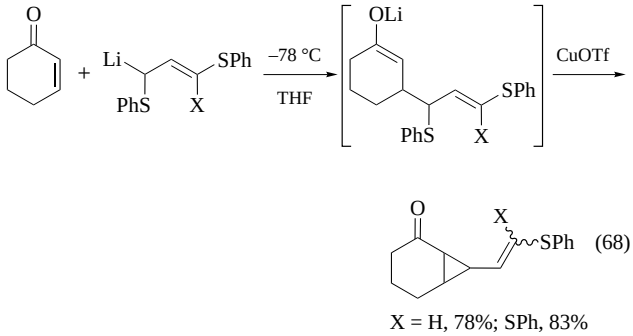
(66)

Cyclopropanation of Enones. Conjugate addition of lithium tris(phenylthio)methide[44] to α,β-unsaturated ketones produces enolates that cyclize to bis(phenylthio)cyclopropyl ketones at −78 °C upon treatment with nearly one equivalent of $(CuOTf)_2{\cdot}C_6H_6$, i.e. 1.9 equivalents of Cu^I (eq 67).[45] The mild conditions that suffice to bring about nucleophilic displacement of thiophenoxide in the presence of CuOTf are especially noteworthy. In view of the requirement for more than one equivalent of Cu^I to achieve Grob-type fragmentation of β-[bis(phenylthio)methyl]alkoxides (see eq 58), it seems likely, although as yet unproven, that one equivalent of Cu^I coordinates strongly with the enolate oxygen and that a second equivalent of Cu^I is required to activate the thiophenoxide leaving group.



(67)

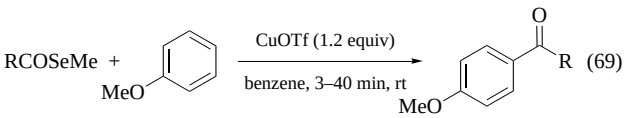
Vinylcyclopropanation of Enones. Conjugate addition of sulfur-stabilized allyl carbanions to α,β-unsaturated ketones produces enolates that cyclize to vinylcyclopropyl ketones upon treatment with nearly one equivalent of $(CuOTf)_2{\cdot}C_6H_6$, i.e. 1.9 equivalents of Cu^I (eq 68).[45]



(68)

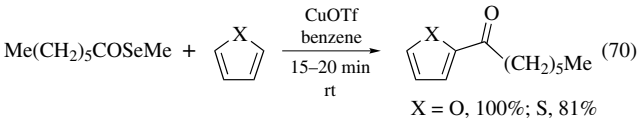
X = H, 78%; SPh, 83%

Friedel–Crafts Acylation with Thio- or Selenoesters. Methylseleno esters are readily available in excellent yields by the reaction of dimethylaluminum methylselenolate with *O*-alkyl esters.[37] These selenoesters will acylate reactive arenes (eq 69) and heterocyclic compounds (eq 70) when activated by CuOTf, a selenophilic Lewis acid.[37] Of the potential activating metal salts tested, $(CuOTf)_2{\cdot}C_6H_6$ is uniquely effective. Mercury(II) or copper(I) trifluoroacetates that are partially organic-soluble, as well as the corresponding chlorides, silver nitrate, and copper(I) oxide that are not organic-soluble, all failed to promote any acylation. The highly reactive CuOTf–benzene complex, in dramatic contrast, was found to readily promote the acylations in benzene solution within minutes at room temperature. The presence of vinyl and keto groups is tolerated by the reaction, and while the alkyl- and vinyl-substituted derivatives afford *para* substitution only, a 2:1 mixture of *para* and *ortho* substitution occurs with the methylseleno ester of levulinic acid. Acylation of toluene is sluggish. Excellent yields of 2-acylfurans, -thiophenes, and -pyrroles are generated by this new variant of the Friedel–Crafts acylation reaction (eq 70). An intramolecular version of this reaction was shown to generate 1-tetralone from the methylseleno ester of γ-phenylbutyric acid (eq 71).[37]



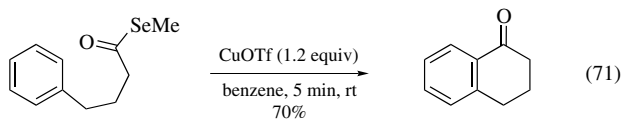
(69)

R = $(CH_2)_5Me$	81%
R = $CH_2CH_2CH{=}CH_2$	63%
R = CH_2CH_2COMe	60%



(70)

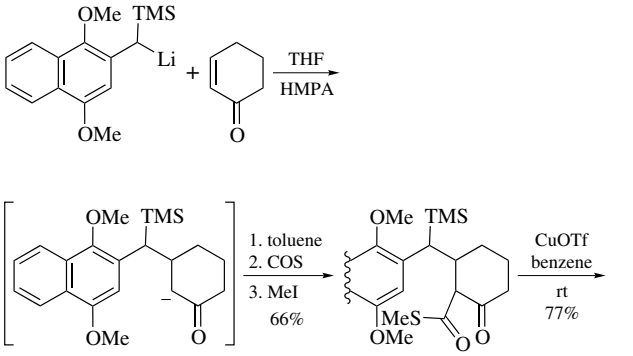
X = O, 100%; S, 81%
NH, 64%



(71)

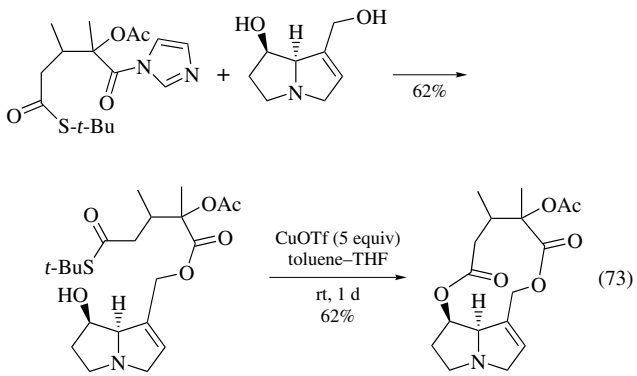
Notwithstanding a prior claim that methylthio esters react only sluggishly under these conditions,[37] such a variant proved effective for a short synthesis of the 4-demethoxy-11-deoxyanthracycline skeleton (eq 72).[46] This is especially significant

because methylthio esters are available by an efficient C–C connective process involving *C*-acylation of ketone lithium enolates with carbon oxysulfide (COS) followed by *S*-methylation with iodomethane.[46] For the deoxyanthracycline synthesis, the requisite enolate was generated by 1,4-addition of a silyl-stabilized benzyllithium derivative to 2-cyclohexenone. Treatment of the methylseleno ester with $(CuOTf)_2{\cdot}C_6H_6$ in benzene, according to the method employed with analogous seleno esters,[37] results in efficient cyclization to deliver a tetracyclic diketone in good yield.



(72)

***O*-Acylation with Thioesters.** Activation of a thioester with $(CuOTf)_2{\cdot}C_6H_6$ was exploited as a key step in the synthesis of a macrocyclic pyrrolizidine alkaloid ester (eq 73).[47] Since thioesters are relatively unreactive acylating agents, a highly functionalized imidazolide containing acetate and *t*-butyl thioester groups selectively acylated only the primary hydroxyl in the presence of the secondary hydroxyl group in (+)-retronecine. Completion of the synthesis required activation of the *t*-butylthio ester. mercury (II) trifluroacelate, that had proven effective for the synthesis of several natural products by lactonization,[48,49] failed to promote any lactonization in the present case.[47] Similarly, mercury(II) and cadmium chloride, that have proven effective for promoting lactonizations,[49] had no effect in the present case. Even copper(I) trifluoroacetate failed to induce the crucial lactonization. In contrast, CuOTf was uniquely effective for inducing the requisite macrolactonization by activating the thioester.



(73)

First Update

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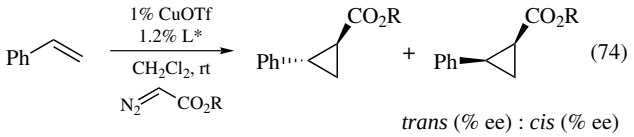
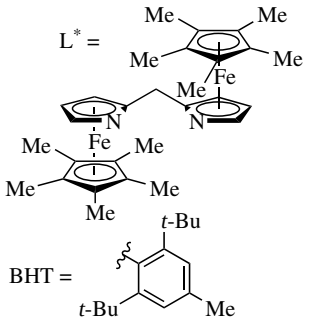
Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France

Asymmetric Copper-catalyzed Cyclopropanation with Diazo Compounds. Asymmetric intermolecular cyclopropanation using diazoacetates has been extensively studied in the last decade. Seminal work[9,50,51] has inspired the development of a large number of chiral catalysts derived from the most active copper salts CuOTf and tetrakis(acetonitrile)copper(I) hexafluorophosphate ($CuPF_6$), and generally C_2-symmetric bidentate ligands.[52] High enantioselectivities and *trans*-diastereoselectivities are easily accessible, the latter being also dependant on the bulk of the ester (eq 74).[53] Mechanistic investigations using DFT calculations are in accordance with the involvement of a concerted addition of the metallacarbene into the alkene substrate and have elucidated the ligand-substrate interactions governing the selectivities.[54]

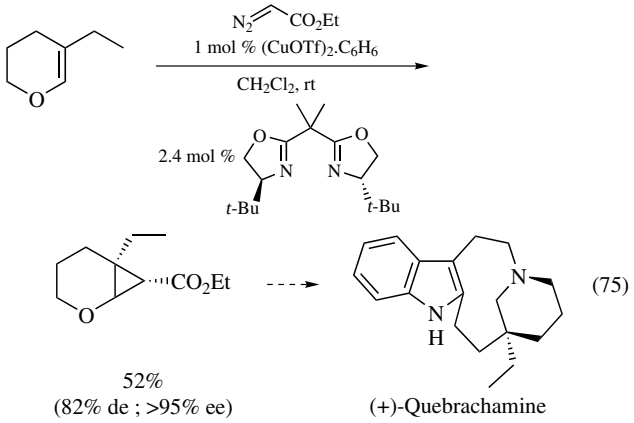


(74)

	trans (% ee) : *cis* (% ee)
R = OEt	76 (73) : 24 (44)
R = O-*t*-Bu	86 (87) : 14 (82)
R = BHT	96 (94) : 4

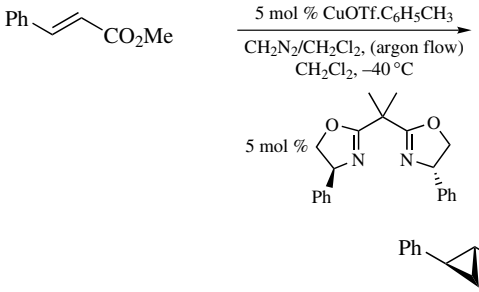


The large synthetic scope of the copper-catalyzed asymmetric cyclopropanation is illustrated by the use of Evans bis(oxazoline) with CuOTf which allows efficient transformation of a cyclic enol ether in the context of a total synthesis of (+)-quebrachamine (eq 75).[55]



(75)

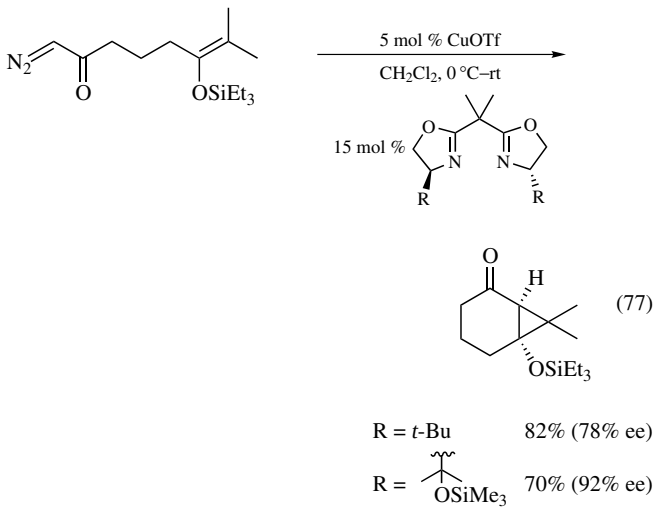
Chiral bis(oxazoline)-CuOTf complexes also have been found to catalyze enantioselective cyclopropanation with diazomethane (eq 76)[56] and (trimethylsilyl)diazomethane,[57] the latter giving rise to higher diastereoselectivities particularly in the case of $CuPF_6$. Copper catalysts are, however, of no help with donor-acceptor diazo reagents such as aryl- and vinyldiazoesters, which are preferentially transferred with very good selectivities in the presence of $Rh_2(DOSP)_4$.[58]



(76)

80% (72% ee)

Enantioselective intramolecular cyclopropanation is also catalyzed by chiral copper complexes, leading to the exclusive formation of the *cis* isomer with five- and six-membered rings. Both CuOTf and $CuPF_6$ can be employed, $CuPF_6$ being particularly efficient in the case of diazo acetate derivatives for the formation of medium to large rings.[59] Diazoketones were found to add with good enantioselectivities to enol silyl ether using bis(oxazoline) ligands (eq 77).[60]

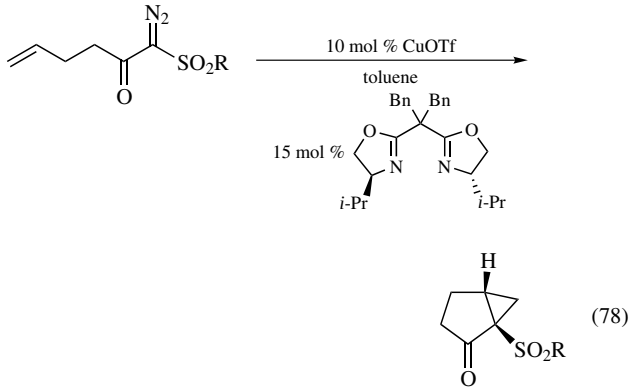


(77)

R = *t*-Bu 82% (78% ee)

R = $OSiMe_3$ 70% (92% ee)

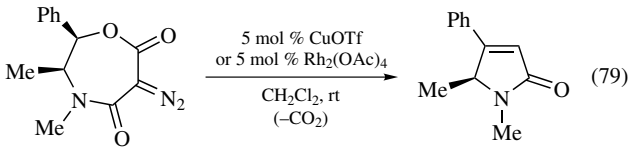
Recently, it was found that chiral bis(oxazoline)-CuOTf complexes are also efficient catalysts in the case of α-diazo β-keto sulfones whose bulk has a significant influence on the enantioselectivity (eq 78).[61] The modest results observed with the parent α-diazo β-keto esters could be attributed to the lack of this steric element.



(78)

R = Ph 61% (73% ee)
R = Mes 87% (93% ee)

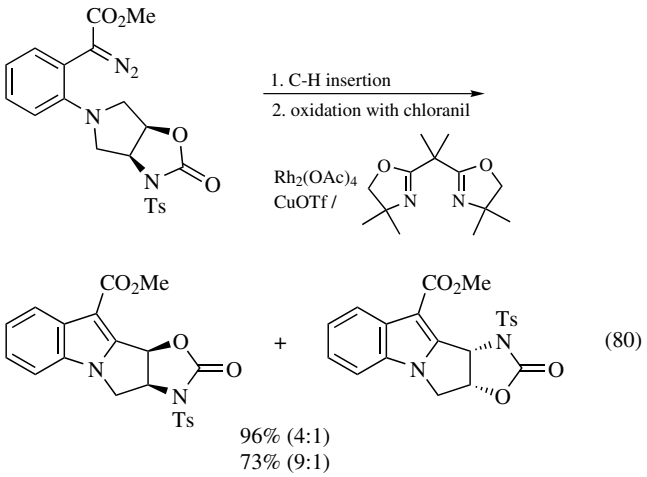
Copper-catalyzed X-H Insertions. Functionalization of alkanes involving insertion into C-H bonds of carbenes generated from diazo compounds is preferentially catalyzed by rhodium(II) carboxylate and carboxamidate complexes.[62] In some cases, however, copper catalysts can provide interesting alternatives. CuOTf is as efficient as rhodium(II) acetate for catalyzing the transformation of a 6-diazooxazepanedione into a 2-pyrrolone (eq 79).[63]



(79)

95%

CuOTf is also the catalyst of choice for the synthesis of a 1,2-aziridinomitosene.[64] While initial asymmetric intramolecular C-H insertions applied to a protected diol provided modest results (diastereomeric ratios up to 3.9:1),[64a,b] use of a CuOTf-bis(oxazoline) complex allowed a more chemoselective intramolecular C-H insertion than that catalyzed by $Rh_2(OAc)_4$ in the case of the cyclic *N*-(tosyl)carbamate (eq 80).[64c]

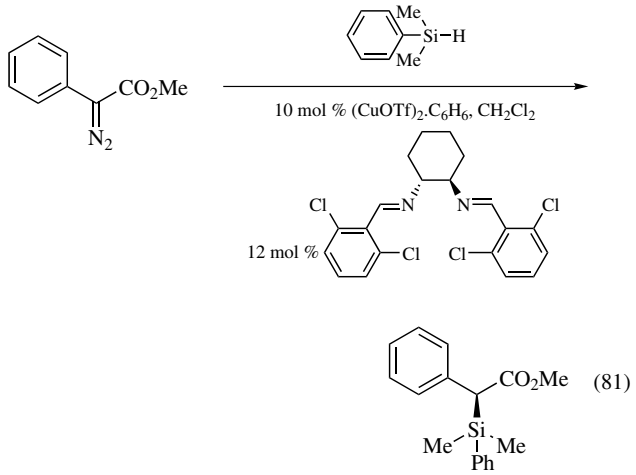


(80)

96% (4:1)
73% (9:1)

Copper complexes are also able to catalyze the insertion of a carbene into a silicon-hydrogen bond.[65] Associated with C_2-symmetric Schiff bases, CuOTf allows the formation of chiral

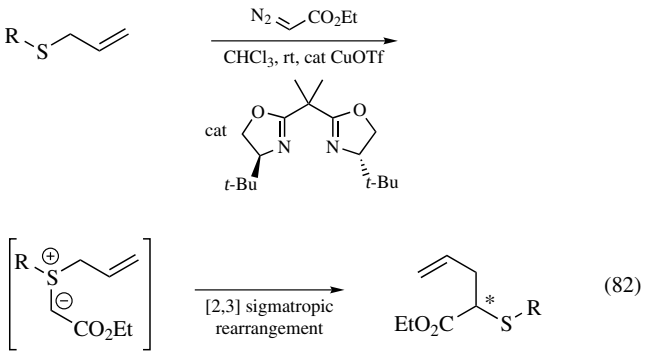
silanes with good enantioselectivity (eq 81).[65b] $CuPF_6$ can also be used while copper(II) trifluoromethanesulfonate, although found to be as efficient as $Rh_2(OAc)_4$ in the analogous achiral process,[65a] gives lower levels of selectivity.



(81)

88% (83% ee)

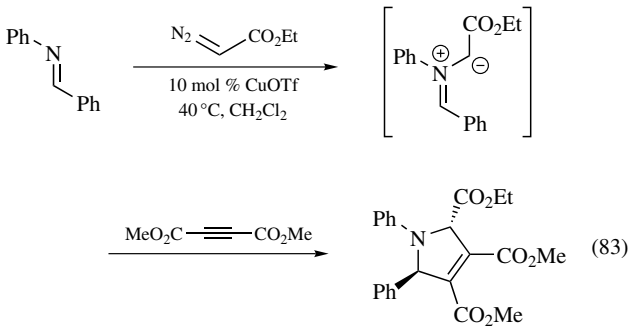
Ylide Formation. Transition-metal catalyzed decomposition of diazo compounds in the presence of heteroatoms allows the generation of ylide species. CuOTf catalyzes this reaction starting from ethyl diazoacetate and allylic sulfides or selenides, albeit with lower efficiency than rhodium complexes.[66] The resulting ylide undergoes a spontaneous [2,3] sigmatropic rearrangement. Use of a CuOTf-bis(oxazoline) complex affords low levels of selectivity[66] but the latter is improved starting from (+)-allyl menthyl sulfide (eq 82).[66b] The modest results are explained in terms of poor discrimination of the heterotopic lone pairs of sulfur by the catalysts.[66b] A comparitive study between trimethylsilyldiazomethane and ethyl diazoacetate demonstrates that the former is more reactive in the same tandem ylide formation-[2,3] sigmatropic rearrangement.[67]



(82)

R = Ph 59% (14% ee)
R = (+)-menthyl 72% (60% ee)

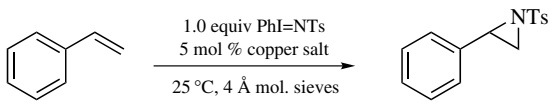
Use of an imine in conjunction with diazoacetates allows the formation of an azomethine ylide intermediate that can undergo a 1,3-dipolar cycloaddition with a suitable dipolarophile. Based on this strategy, CuOTf efficiently catalyzed a three-component assembly reaction for the synthesis of 2,5-*trans*-pyrrolidines using dimethyl acetylenedicarboxylate (eq 83).[68] A large variety of imines and electron-deficient alkenes can be used to generate highly substituted pyrrolidines stereospecifically with respect to the olefin geometry and with modest to good *endo:exo* facial selectivity. The corresponding carbonyl ylide is also generated with *o*-(methoxycarbonyl)-*α*-diazoacetophenone following this strategy.[69] 1,3-Dipolar cycloadditions with *N*-alkylmaleimides are catalyzed by CuOTf, in some cases in association with ytterbium triflate, with very good *endo*-selectivity. However, unlike the preceding case with imines, $Rh_2(OAc)_4$ gives higher yields and selectivities.



(83)

91%
dr >20:1

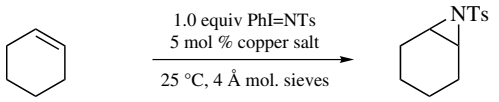
Copper-catalyzed Aziridination. Developed by analogy with the parent copper-catalyzed cyclopropanation, the copper-catalyzed aziridination of olefins[70] has become a method of choice for the synthesis of synthetically useful aziridines.[71] Pioneering studies[72] have revealed the great ability of cationic Cu(I) salts such as CuOTf or the more stable and easily handled tetrakis(acetonitrile) copper(I) perchlorate and $CuPF_6$ to catalyze the aziridination of electron rich, electron poor, or nonfunctionalized alkenes. Copper(II) complexes can also be used (eqs 84 and 85). This process involves a hypervalent iodine(III) reagent as the nitrogen source with [*N*-(*p*-tolylsulfonyl)imino]phenyliodane (PhI=NTs)[73] being the most commonly used. Mechanistic investigations have demonstrated the involvement of a nitrene species generated from the iminoiodane and bound to a copper(III) complex. Depending on the substrate, the nitrene transfer onto the olefin then occurs via two competitive pathways : a concerted addition of a singlet nitrene or a stepwise radical pathway involving a triplet species.[74]



(84)

5.0 equiv

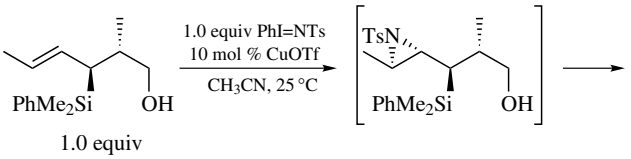
copper salt	
$CuClO_4$	90%
CuOTf	92%
$Cu(OTf)_2$	92%



(85)

5.0 equiv copper salt	
$CuClO_4$	54%
CuOTf	50%
$Cu(OTf)_2$	60%

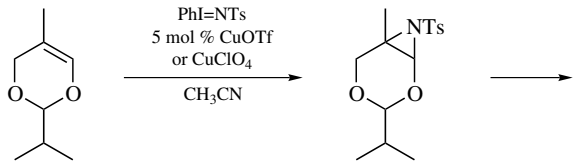
An interesting application of copper-catalyzed aziridination is the preparation of (*E*)-olefin dipeptide isosteres based on a diastereoselective nitrene transfer onto chiral (*E*)-crotylsilanes (eq 86).[75] CuOTf catalyzes the formation of an aziridine whose rearrangement after spontaneous desilylation affords allylamines. Excellent levels of acyclic stereocontrol can be achieved via a hydroxyl-assisted aziridination. Copper-catalyzed aziridination of enol ethers also leads to aziridines that undergo spontaneous rearrangement. Thus, CuOTf and particularly $CuClO_4$ mediate the formation of an α-methylserinal derivative from a 5-methyl-4*H*-1,3-dioxin (eq 87).[76]



1.0 equiv

(86)

64% (based on cons. SM)
>95% de

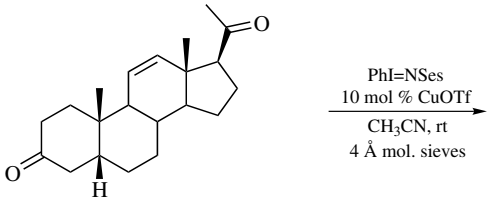


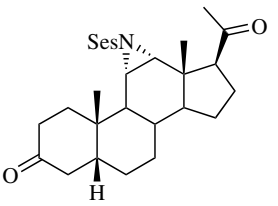
1.0 equiv

(87)

$CuClO_4$	60%
CuOTf	34%

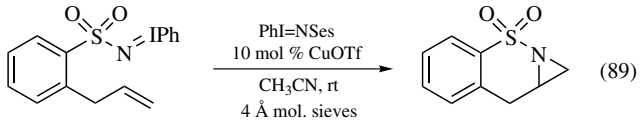
Earlier developments of the copper-catalyzed aziridination of olefins have been limited to the use of PhI=NTs. In order to enhance the efficiency and the scope of the process, other iminoiodanes have been described.[77] CuOTf thus mediates the formation of *N*-(Ses)aziridines starting from {*N*-[2-(trimethylsilyl)ethanesulfonyl]imino}phenyliodane (eq 88).[77b,78] CuOTf also catalyzes the intramolecular aziridination of olefins from unsaturated iminoiodanes, allowing access to substituted cyclic sulfonamides (eq 89).[79] More interestingly, the copper-catalyzed aziridination can be performed directly from the corresponding sulfonamide in the presence of iodosylbenzene thereby avoiding the troublesome preparation of the difficult-to-handle iminoiodanes.[80]





(88)

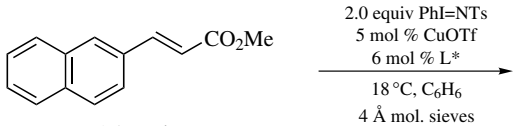
53%



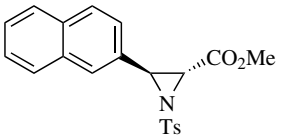
(89)

60%

As for copper-catalyzed cyclopropanation, a large number of C_2-symmetric bidentate ligands has been developed for the asymmetric aziridination of olefins.[70a] Chiral bis(oxazoline)-CuOTf complexes are particularly effective for the reaction with *trans* alkenes (eq 90),[9,81] while bis(benzylidenediamino)cyclohexane derivatives afford high enantioselectivity with *cis* olefins (eq 91).[82] In the latter case, the nature of the substituents at the *ortho* position strongly influences the catalyst lifetime and the selectivity, the best results being obtained with ligands derived from 2,6-dichlorobenzaldehyde. Both types of ligand have been applied with moderate success to the copper-catalyzed aziridination of enol ethers for the preparation of optically active α-amino ketones, CuOTf and $Cu(OTf)_2$ giving lower yields and selectivities than $CuPF_6$.[83]

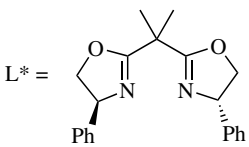


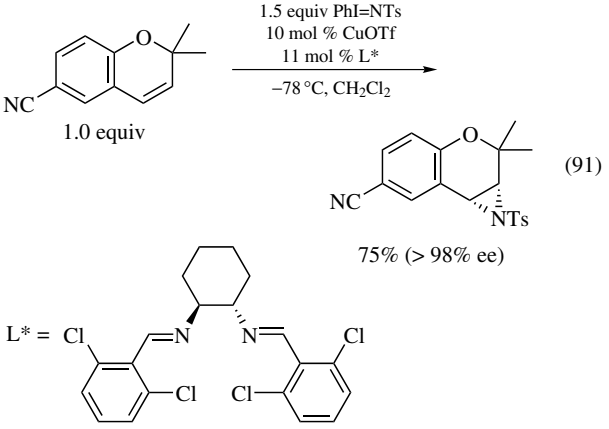
1.0 equiv



(90)

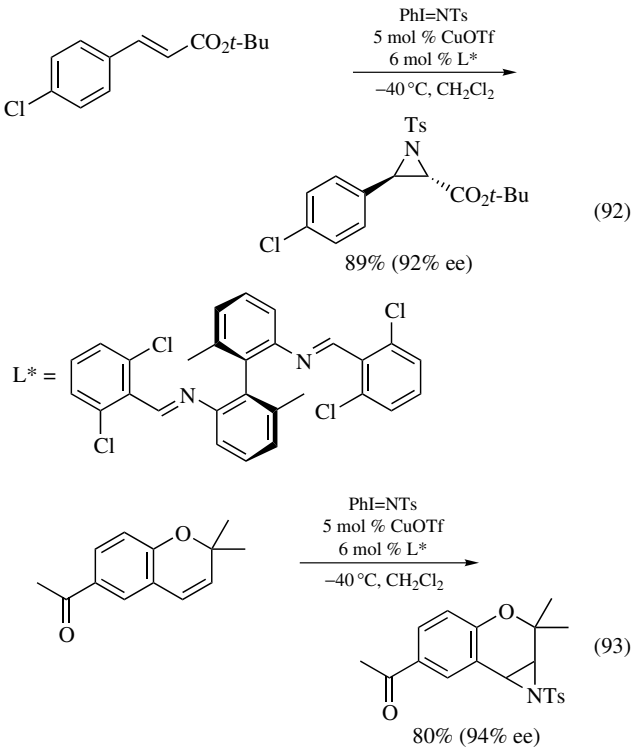
73% (96% ee)





(91)

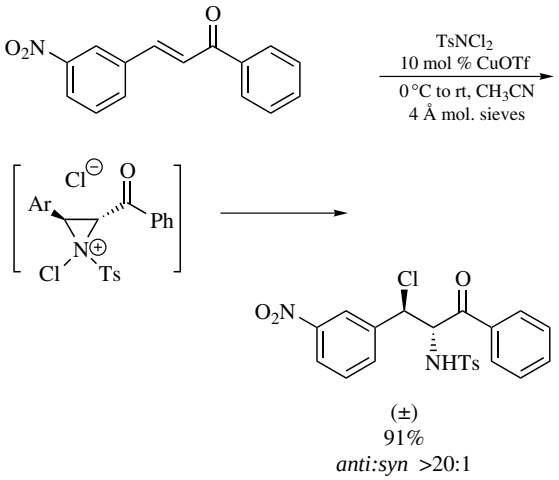
Chiral biaryl Schiff base-CuOTf complexes also efficiently catalyze asymmetric aziridination.[84] *ortho* Substituents prove once more to be crucial since ligands derived from 2,6-disubstituted benzaldehyde and particularly from 2,6-dichlorobenzaldehyde provide, by reaction with CuOTf, monomeric species of high reactivity and selectivity. Under these conditions, asymmetric aziridination of *trans*- and *cis*-alkenes occurs with very good enantioselectivities (eqs 92 and 93).



(92)

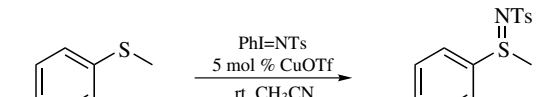
(93)

Chloramine-T[85a,b] and bromamine-T[85c] can also be used as the nitrene source in the copper-catalyzed aziridination but the transfer to olefins occurs with less efficiency. In this context, bromine[86a] and iodine[86b] are better catalysts. However, CuOTf is optimal for the catalytic aminohalogenation of cinnamates or α,β-unsaturated ketones using a combination of *N,N*-dichloro-*p*-nitrobenzenesulfonamide/sodium *p*-nitrobenzenesulfonamidate[87a] or *N,N*-dichloro-*p*-toluenesulfonamide.[87b] The reaction probably proceeds via an aziridinium intermediate which best explains the stereoselective formation of *trans* isomers with excellent regioselectivities (eq 94).

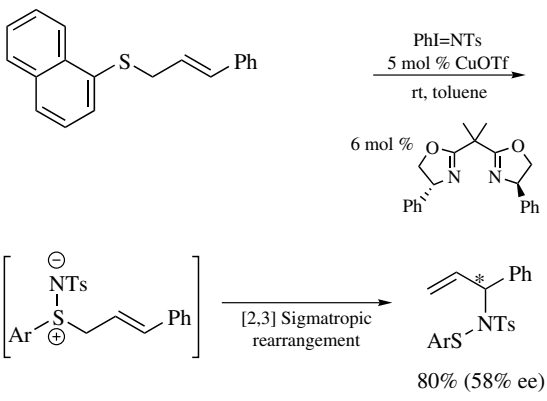


(94)

Catalytic Nitrene Transfer to Heteroatoms. The experimental procedure described above for the copper-catalyzed aziridination of olefins can be applied to the imidation of sulfides, where CuOTf in conjunction with PhI=NTs mediates the formation of sulfimides in good yields (eq 95).[88] Spontaneous [2,3] sigmatropic rearrangements occur in the case of allylic sulfides. Chiral bis(oxazoline)-CuOTf complexes catalyze both reactions with acceptable enantioselectivities (eq 96). Chloramine-T is also a suitable but less efficient nitrene precursor.[88,89] Selenides undergo the same catalytic asymmetric imidation to afford selenimides albeit with lower yields and enantioselectivities.[90]



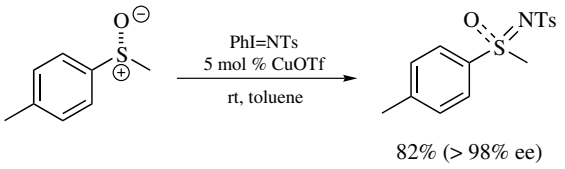
(95)



(96)

The same procedure successfully transforms sulfoxides to sulfoximines.[91] CuOTf[91a] and $Cu(OTf)_2$[91b] are effective catalysts

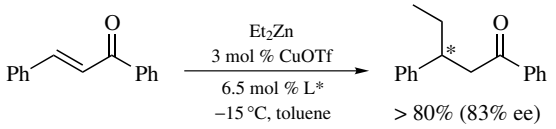
although the former does not operate with ferrocenylsulfoxides.[91c] Complete retention of configuration is observed with enantiopure sulfoxides (eq 97).



(97)

82% (> 98% ee)

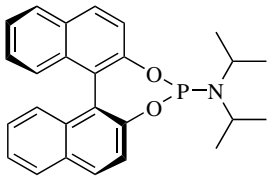
Conjugate Addition to α,β-Enones. There has been a great surge of interest over the last decade in the use of copper(I) and (II) salts in general and CuOTf in particular as catalysts for conjugate addition, asymmetric or not, of organometallics to α,β-unsaturated ketones and related systems. Asymmetric conjugate addition (ACA) of diethylzinc to an acyclic α,β-unsaturated ketone is achieved in high yield (< 80%) and high ee (83%) in the presence of catalytic CuOTf and a chiral phosphorus amidite derived from (*S*)-2,2′-binaphthol (eq 98).[92] The same reaction conditions applied to cyclohexenone give a similar yield of conjugate addition product but only 60% ee (eq 99).

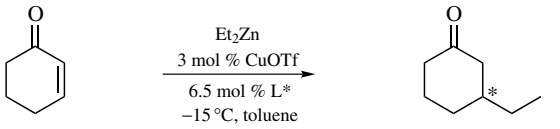


(98)

> 80% (83% ee)

L* =

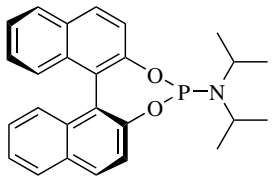




(99)

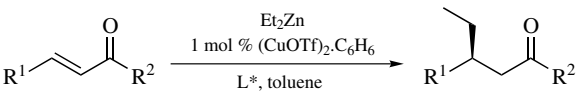
> 80% (60% ee)

L*=



An X-ray crystallographic study of the complex formed by copper and the *N,N*-dimethyl analog of the chiral ligand shows that three of the latter are bound to copper to give a C_3-symmetrical unit. Use of $Cu(OTf)_2$ for the addition reaction gives slightly better ee's, both for the cyclic and noncyclic enones but it is conjectured that the Cu(II) complex is reduced in situ to the Cu(I) complex, the actual reactive species. The use of copper triflate salts for complexation with the amidite ligands has the added advantage of providing homogeneous catalyst solutions.

Generally better ee's (typically 90–98%) for the same reaction with a variety of acyclic enones are obtained using a different 1,1′-binaphthyl chiral ligand, that is, a *P,N*-ligand in which the amine is transformed to the pyridine-2-carboxamide.[93] The CuOTf-benzene complex has been found to be the best copper catalyst for these reactions. A noteworthy observation is that the acyclic enone having only aliphatic substituents (R^1 = *i*-Pr, $R^2 = CH_3$) gives a highly satisfying ee (86%) with this ligand catalyst, although the isolated yield of conjugate addition product is only moderate (53%) (eq 100).

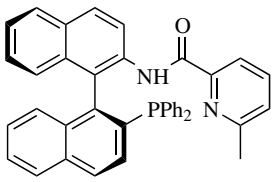


(100)

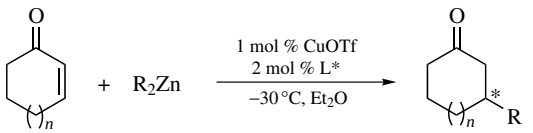
R^1 = Ph, 4-MeO-Ph, 4-Cl-Ph, *i*-Pr
R^2 = Ph, 4-MeO-Ph, 4-Cl-Ph, Me

R^1 = *i*-Pr, R^2 = Me
53% (86% ee)

L* =



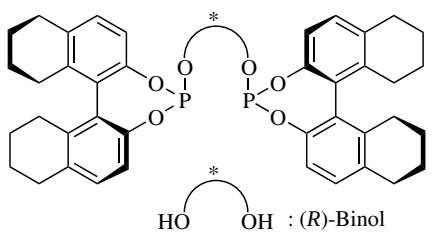
An even more effective chiral ligand for the CuOTf catalyzed conjugate addition of dialkylzinc reagents to cyclic enones is the diphosphite derivative of H_8-binaphthol in which two units of binolate are bridged with a 2,2′-biarylate scaffold (eq 101).[94] Not only cyclohexenone and cycloheptenone but also cyclopentenone, generally considered more resistant to conjugate addition, give high yields (90 to >99%) of 1,4-products and exceptionally high ee's with Et_2Zn (96 to >98%). Less reactive Me_2Zn also gives satisfactory results with cyclohexenone and cycloheptenone though the yield and ee are somewhat low (22% and 21%, respectively) when CuOTf is used to catalyze the ACA to cyclopentenone. The ee can be pushed up to 68% (with no change in product yield) when the copper source is $Cu(OTf)_2$. Contrary to practically all the ACA reactions catalyzed by copper described so far, the coordinating diethyl ether solvent generally gives superior results with this chiral ligand compared to the noncoordinating solvents toluene or dichloromethane.



(101)

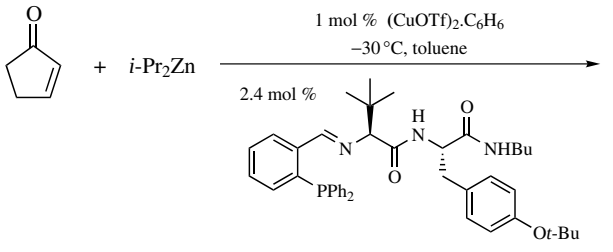
n = 0, 1, 2 R = Me, Et

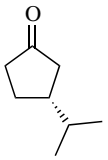
L* =



: (*R*)-Binol

Another family of chiral ligands useful in catalyzing ACA to a variety of substrates in conjunction with CuOTf consists of the peptide-based arylphosphine Schiff bases. These modular ligands can be easily modified structurally in order to fine tune their catalytic activity as a function of the substrate. Thus, while cyclopentenone generally reacts poorly with alkylzinc reagents, especially $(i\text{-Pr})_2Zn$, optimization studies permitted development of a chiral peptide ligand which allows ACA of these two entities with 94% yield and 85% ee (eq 102).[95]

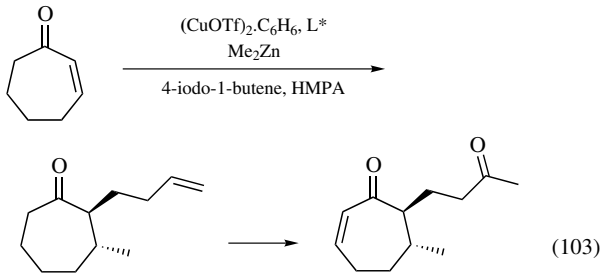




(102)

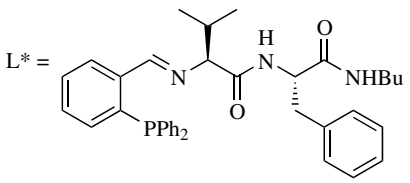
94% (85% ee)

The zinc enolate formed as an intermediate in these conjugate addition reactions can be trapped by an electrophile in situ to provide further functionalization of the substrate. This is demonstrated by the synthesis of the anticancer agent clavularin B (eq 103). Sequential conjugate addition to cycloheptenone of Me_2Zn in the presence of catalytic CuOTf-chiral peptide ligand complex, and enolate alkylation with 4-iodo-1-butene provide the key compound with 97% ee.

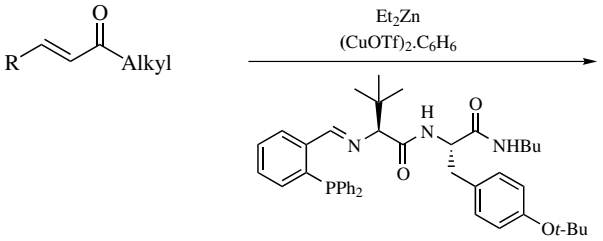


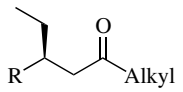
(103)

80% (97% ee) Clavularin B



Related chiral phosphine peptide ligands have been successfully utilized for ACA to acyclic aryl and aliphatic enones (eq 104),[96] trisubstituted cyclic enones (eq 105),[97] cyclic nitroalkenes (from which α-substituted ketones can be prepared via a Nef reaction) (eq 106),[98] and unsaturated *N*-acyloxazolidinones (eq 107).[99] The latter substrates are particularly interesting since they allow access to derivatives (acids, esters, and amides) which cannot be obtained by direct copper-catalyzed ACA to their unsaturated precursors.

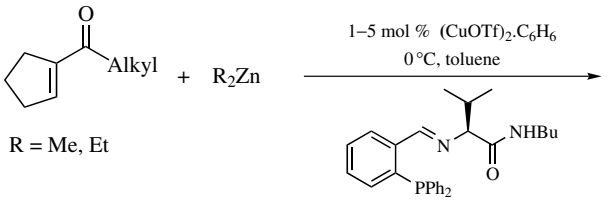


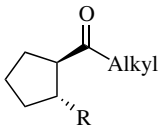


(104)

> 90% ee

R = Ph, 4-MeO-Ph, 4-NO_2-Ph, 4-CF_3-Ph, Me, *i*-Pr , *n*-pent, AcO

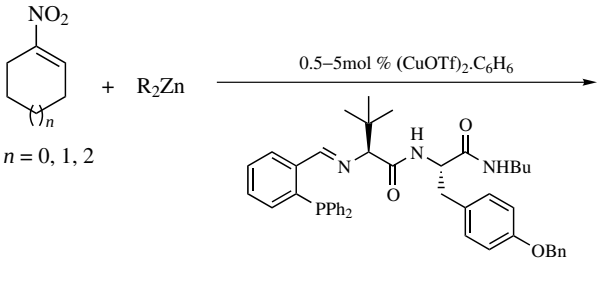


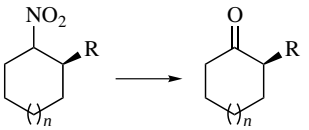


(105)

> 95% ee

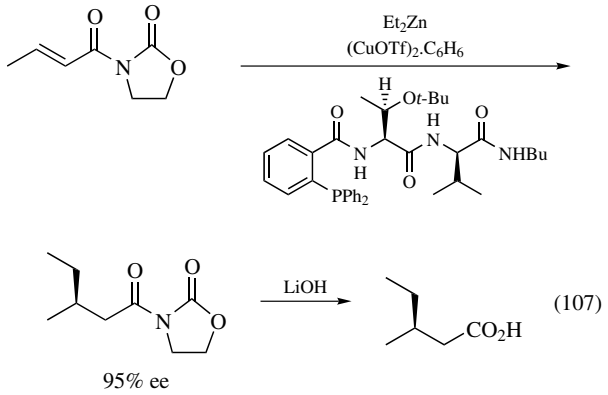
R = Me, Et



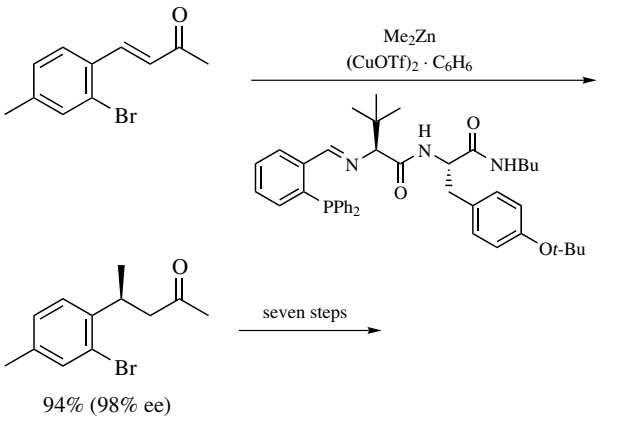


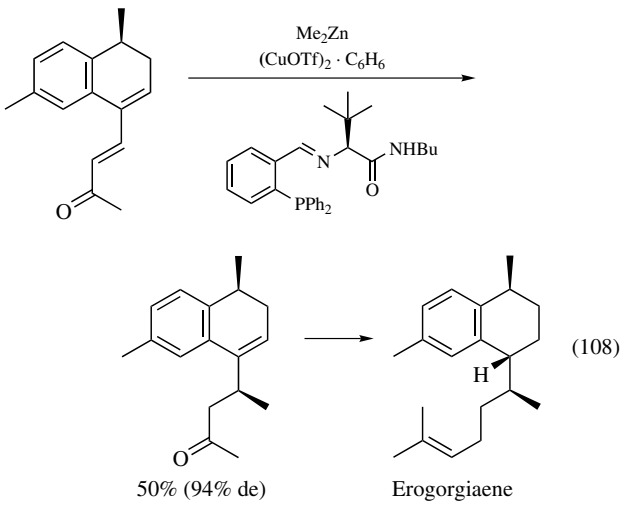
(106)

It should be noted that optimization studies revealed that replacement of the imine function of the chiral peptide ligand by a carboxamide leads to much more satisfactory enantioselection. The efficiency and high stereoselectivity of the CuOTf-chiral peptide ligand complex catalyzed ACA of dialkylzinc to acyclic enones have been demonstrated by the total synthesis of erogorgiaene for which two separate conjugate additions of Me_2Zn, employing two different ligands, are necessary (eq 108).[100]



(107)

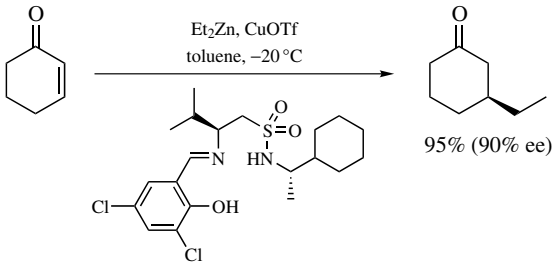




(108)

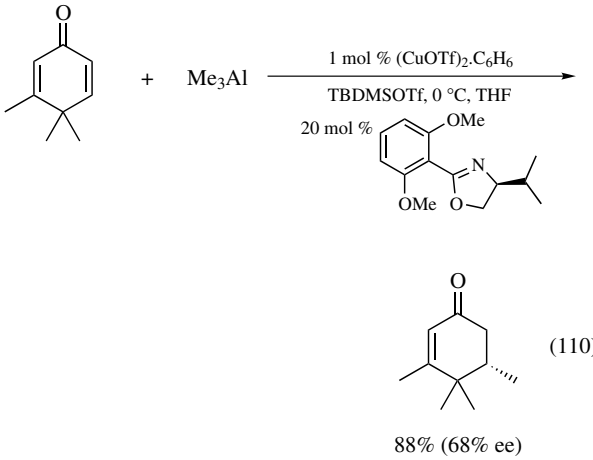
Another family of chiral ligands, structurally related to the aryl Schiff bases of eqs 102–105, has been described for the CuOTf-catalyzed ACA of Et_2Zn to enones. In this case, the peptide fragment is replaced by a monosubstituted sulfonamide while the *ortho*-diphenylphosphine group is replaced by a hydroxyl group.[101] The modular nature of these catalysts makes them amenable to parallel synthesis allowing efficient screening for optimized structures. While an efficient ligand of this type can be found which, in the presence of catalytic CuOTf, provides high ee's and yields of ACA product with a cyclic enone (eq 109), less satisfactory results have been obtained with acyclic enones.

It is nonetheless noteworthy that replacement of the diphenylphosphine group of the ligands described in eqs 102–105 by a hydroxyl group gives inactive catalysts,[95] contrary to the situation of eq 109. It may be assumed that the sulfonamide group of the latter ligand provides an anchoring point for copper, thereby compensating the loss of complexation with the diphenylphosphine group.



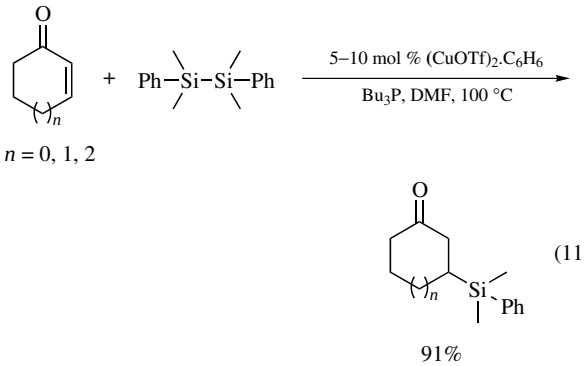
(109)

CuOTf also catalyzes the ACA of trimethylaluminum to cyclohexa-2,5-dienones in the presence of chiral oxazolines (eq 110).[102] The use of an additive (TBDMSOTf) is necessary to obtain good yields and enantioselectivities though the latter do not surpass 68% despite intensive ligand optimization.



(110)

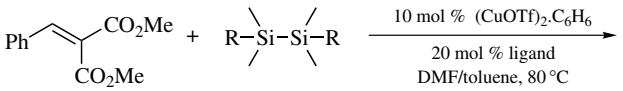
Treatment of a disilane with CuOTf generates a silyl anion which can add in conjugate fashion to α,β-unsaturated carbonyl compounds (eq 111).[103] Optimal conditions consist of heating the reaction mixture in DMF in the presence of tributylphosphine. Absence of the latter gives very low conjugate addition product (20%).

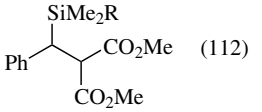


(111)

Conjugate addition to acyclic alkyl and aryl enones is also generally highly efficient.[104] Application of the same reaction conditions to aryl alkylidene malonates provides the corresponding β-silyl malonates in generally good yield (53–84%) (eq 112).

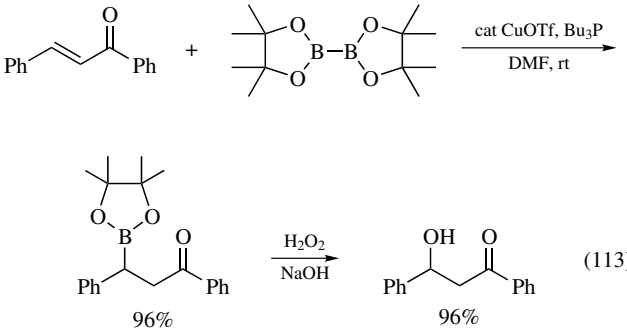
Alkyl alkylidene malonates are not as satisfactory substrates even with higher catalyst loadings (15 mol% CuOTf-benzene complex). Pyridine instead of tributylphosphine can also be used as complexing agent.





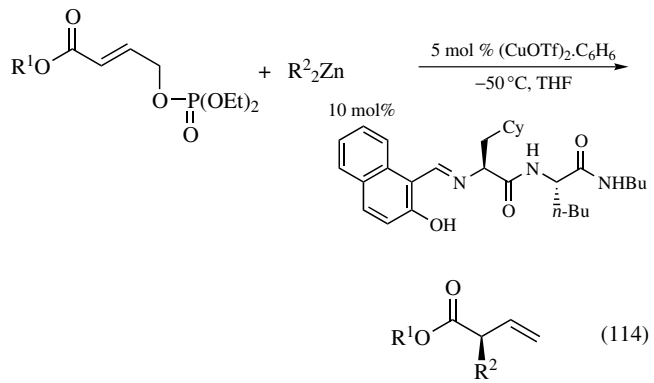
(112)

Analogously, copper(I) salts cleave diboron compounds [e.g., bis(pinacolato)diboron] to give, in the presence of an α,β-enone, the corresponding conjugate boration product (eq 113).[105] In contrast to the silylation procedure, reactions can be run at room temperature both on cyclic and acyclic enones. Subsequent oxidation of the borylated ketone provides the β-hydroxyketone.



(113)

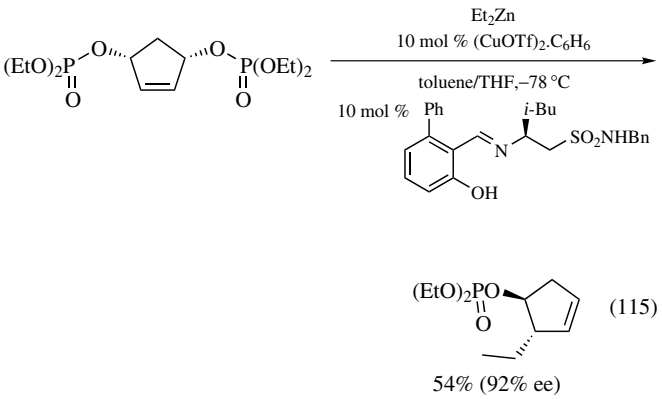
Allylic Alkylations. The chiral imine type ligands used in conjunction with CuOTf to catalyze asymmetric conjugate additions of dialkylzincs have also found use for allylic alkylations of unsaturated substrates. Thus, α,β-unsaturated esters bearing a primary γ-phosphate are regioselectively (S_N2:S_N2' >20:1 for *t*-butyl esters) alkylated in good yield and with high enantioselectivity (generally 90% ee or greater) (eq 114).[106]



(114)

R^1 = Me ; R^2 = Et 93% (95% ee)
R^1 = *t*-Bu ; R^2 = Me 80% (90% ee)

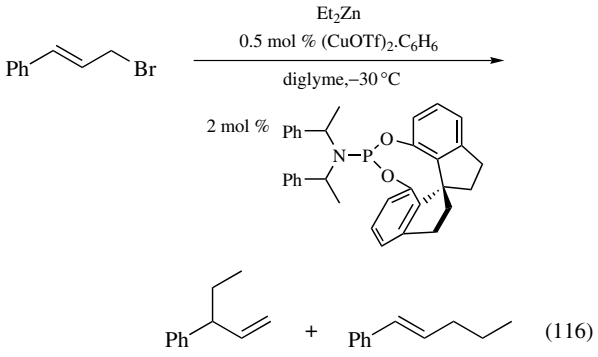
Analogously, desymmetrization of *meso* cyclic allylic bis-(diethylphosphates) is achieved with high regio-, diastereo-, and enantioselectivity by reaction with Et_2Zn in the presence of a preformed chiral Schiff base-CuOTf complex (eq 115).[107] Other copper sources [CuCN and $Cu(OTf)_2$] are less satisfactory. It has been observed that different ligands, while maintaining the same relative configuration, can give preferentially the opposite enantiomer. Me_2Zn and Ph_2Zn are also effective in this reaction. On the other hand, extension of this procedure to the analogous cyclohexene *meso* derivative leads to racemic mixtures, though the diastereoselectivity remains quite high.



(115)

54% (92% ee)

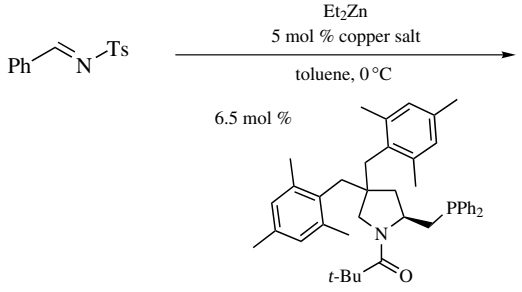
Highly regioselective asymmetric alkylation of cinnamyl halides by dialkylzincs can also be achieved by CuOTf complexed with spiro phosphoramidite or phosphite ligands. For example, using the former type of ligand, reaction of cinnamyl bromide with Et_2Zn gives mainly the S_N2' product (S_N2/S_N2':12/88) with 71% ee (eq 116).[108] With the phosphoramidite ligands CuOTf gives the highest enantioselectivities compared to other copper sources; $Cu(OTf)_2$ is superior in the case of the phosphite ligands.



(116)

62%
88 (71% ee):12

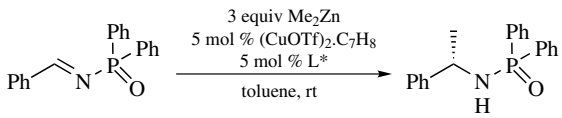
Addition to Imines. CuOTf-catalyzed alkylation of *N*-(activated)imines also proceeds with dialkylzinc reagents. Use of a chiral amidophosphine leads to the asymmetric alkylation of *N*-(*p*-toluenesulfonyl)imines with dimethyl-, diethyl-, and di-*i*-propylzinc in good yields and high enantioselectivities.[109] CuOTf is the most active catalyst but efficiency is optimal with $Cu(OTf)_2$ (eq 117). Chiral binaphthylthiophosphoramides give slightly lower selectivities.[110]



(117)

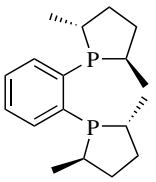
copper salt
$(CuOTf)_2.C_6H_6$: 0.5 h 95% (90% ee)
$Cu(OTf)_2$: 5 h 97% (96% ee)

N-(Phosphinoyl)imines similarly undergo catalytic asymmetric alkylation with Et_2Zn and Me-DuPHOS as the optimal ligand[111] but the lack of reactivity with Me_2Zn has led to the development of improved chiral complexes. Thus, a combination of 3 equiv of Me_2Zn in the presence of a catalytic quantity of the CuOTf-BozPHOS complex affords the corresponding α-methylbenzylamine in high yield and enantioselectivity (eq 118).[112] Under these conditions, several other diorganozinc reagents can be added using CuOTf or $Cu(OTf)_2$.

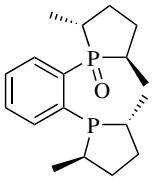


(118)

10 equiv Me_2Zn, L* : Me-DuPHOS 35% (73% ee)
3 equiv Me_2Zn, L* : BozPHOS 87% (97% ee)



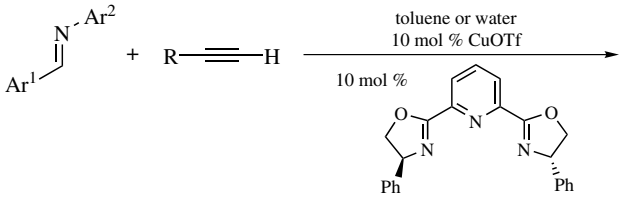
Me-DuPHOS

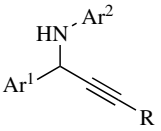


BozPHOS

The Cu(I)-catalyzed direct addition of terminal alkynes to imines generated in situ from aldehydes and amines affords synthetically useful propargylamines. This metal-catalyzed carbon-carbon bond formation is best performed in toluene but water is also a convenient solvent.[113] While the achiral process is mediated by the bimetallic catalytic system $RuCl_3$/CuBr, CuOTf in conjunction with chiral bis(oxazolines) has been found optimal for enantioselective additions (eq 119).

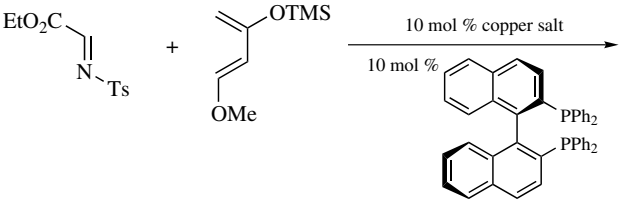
CuOTf is also a catalyst able to mediate enantioselective ene reactions with imines[114] and asymmetric addition of allylic metal compounds to α-imino esters[115] or aza Diels-Alder.[116] In the latter case, CuOTf gives yields and enantioselectivities comparable to those obtained with the other copper(I) salt used in the studies (eq 120).

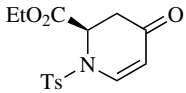




(119)

48–93% (78–96% ee)

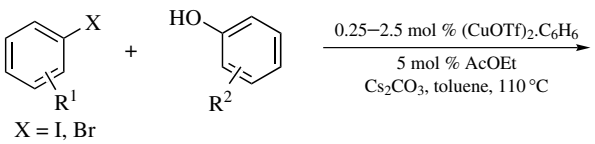


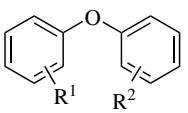


(120)

copper salt
$(CuOTf)_2.C_6H_6$: 60% (61% ee)
$CuClO_4.4MeCN$: 65% (64% ee)

Copper-catalyzed C-O, C-N, and C-S Coupling. While there is an extensive variety of palladium catalysts for C(aryl)-X bond formation (X = O, N, and S), copper complexes have recently gained renewed popularity in these coupling processes.[117] Use of the $(CuOTf)_2$.benzene complex allows the formation of diaryl ethers from aryl bromides or iodides and phenols in very good yields (76–93%) (eq 121).[118] The reaction occurs in toluene in the presence of cesium carbonate as the base and a catalytic quantity of ethyl acetate whose role is probably to increase the solubility of the copper species. In the case of less reactive phenols, yields can be increased by the addition of a stoichiometric amount of carboxylic acid. A slight modification of these conditions has been used in the key diaryl ether formation in the synthesis of verbenachalcone.[119]

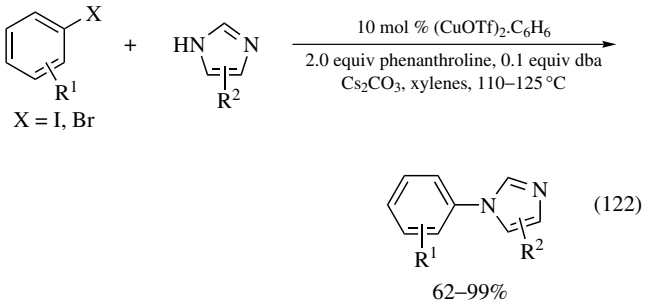




(121)

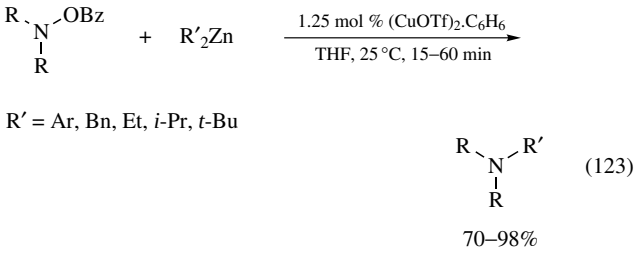
The combination of the $(CuOTf)_2$·benzene complex with Cs_2CO_3 also catalyzes C-N bond formation. Coupling of aryl

halides with imidazoles thus efficiently takes place in the presence of phenanthroline and dibenzylideneacetone(dba) (eq 122).[120a] This procedure has been applied to the *N*-arylation of 5-iodouracil[120b] and histidine[120c] derivatives.



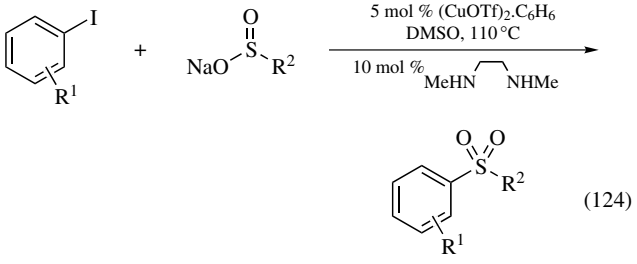
(122)

A promising method for C–N bond construction involves the use of diorganozinc reagents. $(CuOTf)_2$.benzene complex catalyzes under mild conditions the coupling between various *N*,*N*-dialkyl-*O*-acylhydroxylamines and several diaryl- or dialkylzincs that can be generated in situ from the corresponding organolithium or magnesium (eq 123).[121]



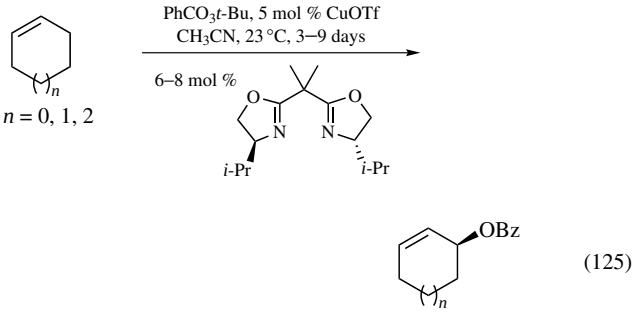
(123)

CuOTf-catalyzed C-S bond formation allows the formation of arylmethyl- and diarylsulfones. The coupling between aryl iodides and sulfinic acid salts proceeds in DMSO in the presence of *N*,*N*′-dimethylethylenediamine to give the sulfones with variable yields (eq 124).[122]



(124)

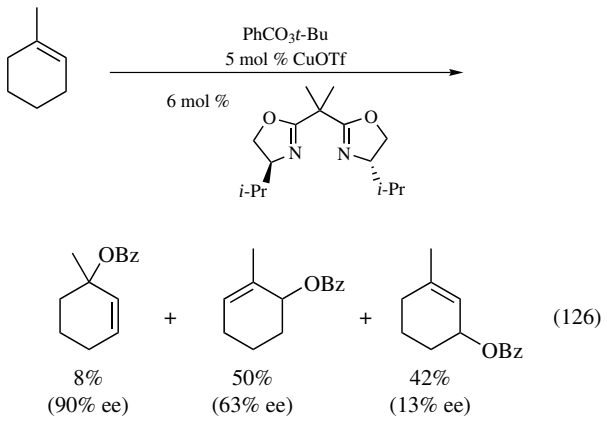
Allylic Oxidation. Chiral CuOTf-bis(oxazoline) complexes catalyze the asymmetric Kharasch acyloxylation of cyclopentene, cyclohexene, and cycloheptene with *t*-butyl perbenzoate with good yields but moderate enantioselectivities (eq 125).[123]



(125)

Running the reaction at lower temperatures sometimes leads to higher ee's at the expense of lower yields and longer reaction times (up to 22 days for cyclopentene). Varying the nature of the C-5 groups on the bis(oxazolines), introducing substituents on the phenyl ring of the perester or using different sources of copper(I) have little positive impact on the overall yield and selectivities of the reaction.[124]

Reaction of 1-methylcyclohexene under basically the same conditions affords a mixture of three regioisomeric allylic oxidation products (eq 126).[123] Interestingly, the isomer formed in the smallest proportion (8%) is obtained with the highest ee (90%). With acyclic alkenes only very modest yields and ee's are obtained.[125]



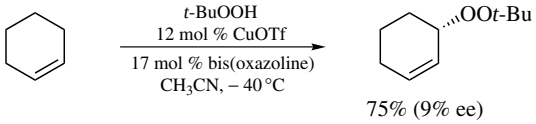
(126)

These allylic oxidation reactions are characterized by very long reaction times, generally measured in days. This situation has been partially remedied by the empirical observation that addition of 5 mol% phenylhydrazine [which serves to reduce Cu(II) to Cu(I) in situ] to the reaction medium greatly accelerates the rate of the reaction (e.g., 5 h instead of 6 days for the allylic oxidation of cyclohexene) with little effect on yields and enantioselectivities. It has been further observed that the presence of 4 Å molecular sieves in the reaction mixture has a positive effect on enantioselectivities (e.g., 86% ee for cyclohexene oxidation vs. 73% ee in absence of molecular sieves).[126]

Structural variants of the chiral bis(oxazoline) ligands have been described for the CuOTf-catalyzed asymmetric Kharasch reaction. Thus, a chiral CuOTf-tris(oxazoline) complex catalyzes the allylic oxidation of cyclopentene in 67% yield and with 66% ee.[127] $Cu(OTf)_2$ is, however, moderately more effective (68% yield, 74% ee). Fluorous bis(oxazolines), in which two

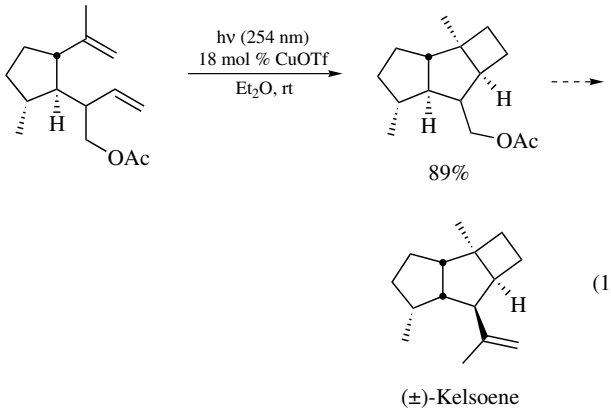
long-chained fluorinated hydrocarbons (C_8F_{17} and $C_{10}F_{21}$) are attached to the bridging methylene group, have been developed for use in fluorous biphasic catalysis and permit allylic oxidation of cyclopentene in 87% yield and with 77% ee.[128]

Replacement of *t*-butyl perbenzoate in the oxidation reaction by *t*-butyl hydroperoxide allows, in the presence of catalytic CuOTf-bis(oxazoline) complex, allylic peroxidation of cyclohexene (eq 127). While the yield is good (75%), the enantioselectivity is quite poor (9% ee).[129] A similar trend (high yield, low ee) is observed for the peroxidation of cyclopentene, α-angelica lactone and allylbenzene.



75% (9% ee) (127)

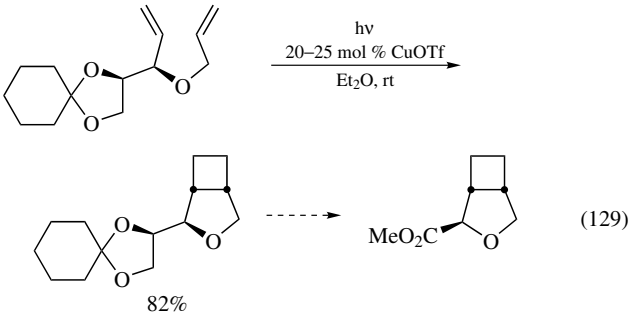
Asymmetric [2 + 2] Photocycloadditions. Intramolecular copper-catalyzed [2 + 2] photocycloaddition is a useful methodology for the preparation of bicyclic cyclobutanes and recent studies deal with its asymmetric version albeit with variable success. Diastereoselective reactions are achieved under the control of stereogenic centers incorporated in the dienic precursors. Both CuOTf[130a] and the more stable and easy to handle $Cu(OTf)_2$[130b,c] are suitable catalysts in this context. In the latter case, it is assumed that the copper(I) species is generated from $Cu(OTf)_2$ under the photochemical conditions.[131] A noteworthy example is the application of the CuOTf-catalyzed [2 + 2] photocycloaddition in the stereoselective total synthesis of the tricyclic sesquiterpene kelsoene (eq 128).[132]



89% (128)

(±)-Kelsoene

Use of *pseudo*-chiral auxiliaries also allows the diastereoselective formation of substituted cyclobutane. Very high diastereoselectivities can be achieved using the concept of chirality transfer from a suitably protected (*R*)-glyceraldehyde derivative. After removal of the auxiliary, enantiomerically pure compounds are obtained (eq 129).[133] However, use of chiral CuOTf complexes does not afford significant enantioselectivity (< 5%).[134]



82% (129)

Related Reagents. Copper(II) Trifluoromethanesulfonate; Copper(I) Iodide; Tetrakis(acetonitrile)copper(I) Hexafluorophosphate; Tetrakis(acetonitrile)copper(I) Perchlorate.

1. (a) Salomon, R. G., *Adv. Chem. Ser.* **1978**, *168*, 174. (b) Salomon, R. G., *Tetrahedron* **1983**, *39*, 485. (c) Salomon, R. G.; Kochi, J. K., *Tetrahedron Lett.* **1973**, 2529.
2. Jenkins, C. L.; Kochi, J. K., *J. Am. Chem. Soc.* **1972**, *94*, 843.
3. (a) Hathaway, B. J.; Holah, D. G.; Postlethwaite, J. D., *J. Chem. Soc.* **1961**, 3215. (b) Kubota, M.; Johnson, D. L., *J. Inorg. Nucl. Chem.* **1967**, *29*, 769.
4. (a) Salomon, R. G.; Kochi, J. K., *J. Chem. Soc., Chem. Commun.* **1972**, 559. (b) Salomon, R. G.; Kochi, J. K., *J. Am. Chem. Soc.* **1973**, *95*, 1889. (c) Dines, M. B., *Separ. Sci.* **1973**, *8*, 661.
5. Cohen, T.; Ruffner, R. J.; Shull, D. W.; Fogel, E. R.; Falck, J. R., *Org. Synth.* **1980**, *59*, 202; *Org. Synth., Coll. Vol.* **1988**, *6*, 737.
6. Salomon, R. G.; Kochi, J. K., *J. Am. Chem. Soc.* **1973**, *95*, 3300.
7. Wiberg, K. B.; Kass, S. R.; Bishop, III, K. C., *J. Am. Chem. Soc.* **1985**, *107*, 996.
8. Lewis, R. T.; Motherwell, W. B., *Tetrahedron Lett.* **1988**, *29*, 5033.
9. (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M., *J. Am. Chem. Soc.* **1991**, *113*, 726. (b) Evans, D. A.; Woerpel, K. A.; Scott, M. J., *Angew. Chem., Int. Ed.* **1992**, *31*, 430.
10. Trecker, D. J.; Foote, R. S., In *Organic Photochemical Synthesis*; Srinivasan, R., Ed.; Wiley: New York, 1971; Vol. 1, p 81.
11. Salomon, R. G.; Kochi, J. K., *J. Am. Chem. Soc.* **1974**, *96*, 1137.
12. Salomon, R. G.; Kochi, J. K., *J. Am. Chem. Soc.* **1973**, *95*, 1889.
13. Salomon, R. G.; Folting, K.; Streib, W. E.; Kochi, J. K., *J. Am. Chem. Soc.* **1974**, *96*, 1145.
14. Evers, J. T. M.; Mackor, A., *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 423.
15. Evers, J. T. M.; Mackor, A., *Tetrahedron Lett.* **1980**, *21*, 415.
16. Spee, T.; Mackor, A., *J. Am. Chem. Soc.* **1981**, *103*, 6901.
17. Evers, J. T. M.; Mackor, A., *Tetrahedron Lett.* **1978**, 2317.
18. Salomon, R. G.; Sinha, A., *Tetrahedron Lett.* **1978**, 1367.
19. Evers, J. T. M.; Mackor, A., *Tetrahedron Lett.* **1978**, 821.
20. (a) Raychaudhuri, S. R.; Ghosh, S.; Salomon, R. G., *J. Am. Chem. Soc.* **1982**, *104*, 6841. (b) Ghosh, S.; Raychaudhuri, S. R.; Salomon, R. G., *J. Org. Chem.* **1987**, *52*, 83.
21. Avasthi, K.; Raychaudhuri, S. R.; Salomon, R. G., *J. Org. Chem.* **1984**, *49*, 4322.
22. Hertel, R.; Mattay, J.; Runsink, J., *J. Am. Chem. Soc.* **1991**, *113*, 657.
23. (a) Salomon, R. G.; Coughlin, D. J.; Easler, E. M., *J. Am. Chem. Soc.* **1979**, *101*, 3961. (b) Salomon, R. G.; Ghosh, S., *Org. Synth.* **1984**, *62*, 125; *Org. Synth., Coll. Vol.* **1990**, *7*, 177. (c) Salomon, R. G.; Coughlin, D. J.; Ghosh, S.; Zagorski, M. G., *J. Am. Chem. Soc.* **1982**, *104*, 998.
24. Salomon, R. G.; Ghosh, S.; Zagorski, M. G.; Reitz, M., *J. Org. Chem.* **1982**, *47*, 829.
25. McMurry, J. E.; Choy, W., *Tetrahedron Lett.* **1980**, *21*, 2477.

26. Avasthi, K.; Salomon, R. G., *J. Org. Chem.* **1986**, *51*, 2556.
27. Salomon, R. G.; Ghosh, S.; Raychaudhuri, S.; Miranti, T. S., *Tetrahedron Lett.* **1984**, *25*, 3167.
28. Hefner, J. G.; Zizelman, P. M.; Durfee, L. D.; Lewandos, G. S., *J. Organomet. Chem.* **1984**, *260*, 369.
29. (a) Cohen, T.; Cristea, I., *J. Org. Chem.* **1975**, *40*, 3649. (b) Cohen, T.; Cristea, I., *J. Am. Chem. Soc.* **1976**, *98*, 748.
30. Cohen, T.; Tirpak, J., *Tetrahedron Lett.* **1975**, 143.
31. Cohen, T.; Herman, G.; Falck, J. R.; Mura, Jr., A. J., *J. Org. Chem.* **1975**, *40*, 812.
32. Kwon, T. W.; Smith, M. B., *Synth. Commun.* **1992**, *22*, 2273.
33. Cohen, T.; Mura, A. J.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R., *J. Org. Chem.* **1976**, *41*, 3218.
34. Corey, E. J.; Seebach, D., *J. Org. Chem.* **1966**, *31*, 4097.
35. Cohen, T.; Kosarych, Z., *Tetrahedron Lett.* **1980**, *21*, 3955.
36. Cohen, T.; Gapinski, R. E.; Hutchins, R. R., *J. Org. Chem.* **1979**, *44*, 3599.
37. (a) Kozikowski, A. P.; Ames, A., *J. Am. Chem. Soc.* **1980**, *102*, 860. (b) Kozikowski, A. P.; Ames, A., *Tetrahedron* **1985**, *41*, 4821.
38. (a) Corey, E. J.; Noyori, R., *Tetrahedron Lett.* **1970**, 311. (b) Corey, E. J.; Erickson, B. W.; Noyori, R., *J. Am. Chem. Soc.* **1971**, *93*, 1724.
39. Cohen, T.; Bennett, D. A.; Mura, A. J., *J. Org. Chem.* **1976**, *41*, 2506.
40. Semmelhack, M. F.; Tomesch, J. C., *J. Org. Chem.* **1977**, *42*, 2657.
41. Cohen, T.; Kuhn, D.; Falck, J. R., *J. Am. Chem. Soc.* **1975**, *97*, 4749.
42. Knapp, S.; Trope, A. F.; Ornaf, R. M., *Tetrahedron Lett.* **1980**, *21*, 4301.
43. Knapp, S.; Trope, A. F.; Theodore, M. S.; Hirata, N.; Barchi, J. J., *J. Org. Chem.* **1984**, *49*, 608.
44. Seebach, D., *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 442.
45. Cohen, T.; Meyers, M., *J. Org. Chem.* **1988**, *53*, 457.
46. Vedejs, E.; Nader, B., *J. Org. Chem.* **1982**, *47*, 3193.
47. Huang, J.; Meinwald, J., *J. Am. Chem. Soc.* **1981**, *103*, 861.
48. (a) Masamune, S., *Aldrichim. Acta* **1978**, *11*, 23. (b) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A., *J. Am. Chem. Soc.* **1975**, *97*, 3513.
49. Masamune, S.; Kamata, S.; Schilling, W., *J. Am. Chem. Soc.* **1975**, *97*, 3515.
50. (a) Fritschi, H.; Leutenegger, U.; Pfaltz, A., *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1005. (b) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A., *Helv. Chim. Acta* **1991**, *74*, 232.
51. (a) Lowenthal, R. E.; Abiko, A.; Masamune, S., *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Lowenthal, R. E.; Masamune, S., *Tetrahedron Lett.* **1991**, *32*, 7373.
52. (a) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B., *Chem. Rev.* **2003**, *103*, 977. (b) Kirmse, W., *Angew. Chem., Int. Ed.* **2003**, *42*, 1088.
53. Lo, M. M. C.; Fu, G. C., *J. Am. Chem. Soc.* **1998**, *120*, 10270.
54. (a) Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L., *J. Am. Chem. Soc.* **2001**, *123*, 7616. (b) Rasmussen, T.; Jensen, J. F.; Østergaard, N.; Tanner, D.; Ziegler, T.; Norrby, P. O., *Chem. Eur. J.* **2002**, *8*, 177.
55. Temme, O.; Taj, S. A.; Andersson, P. G., *J. Org. Chem.* **1998**, *63*, 6007.
56. Charette, A. B.; Janes, M. K.; Lebel, H., *Tetrahedron:Asymmetry* **2003**, *14*, 867.
57. France, M. B.; Milojevich, A. K.; Stitt, T. A.; Kim, A. J., *Tetrahedron Lett.* **2003**, *44*, 9287.
58. Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J., *J. Am. Chem. Soc.* **1996**, *118*, 6897.
59. Doyle, M. P.; Phillips, I. M., *Tetrahedron Lett.* **2001**, *42*, 3155.
60. Tokunoh, R.; Tomiyama, H.; Sodeoka, M.; Shibasaki, M., *Tetrahedron Lett.* **1996**, *37*, 2449.
61. (a) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M., *J. Am. Chem. Soc.* **2003**, *125*, 2860. (b) Honma, M.; Nakada, M., *Tetrahedron Lett.* **2003**, *44*, 9007.
62. Davies, H. M. L.; Beckwith, R. E. J., *Chem Rev.* **2003**, *103*, 2861.
63. Chelucci, G.; Saba, A., *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 78.
64. (a) Lim, H. J.; Sulikowski, G. A., *J. Org. Chem.* **1995**, *60*, 2326. (b) Burgess, K.; Lim, H. J.; Porte, A. M.; Sulikowski, G. A., *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220. (c) Lee, S.; Lee, W. M.; Sulikowski, G. A., *J. Org. Chem.* **1999**, *64*, 4224.
65. (a) Andrey, O.; Landais, Y.; Planchenault, D.; Weber, V., *Tetrahedron* **1995**, *51*, 12083. (b) Dakin, L. A.; Schaus, S. E.; Jacobsen, E. N.; Panek, J. S., *Tetrahedron Lett.* **1998**, *39*, 8947.
66. (a) Nishibayashi, Y.; Ohe, K.; Uemura, S., *J. Chem. Soc., Chem. Commun.* **1995**, 1245. (b) Mc Millen, D. W.; Varga, N.; Reed, B. A.; King, C., *J. Org. Chem.* **2000**, *65*, 2532.
67. Carter, D. S.; Van Vranken, D. L., *Tetrahedron Lett.* **1999**, *40*, 1617.
68. Galliford, C. V.; Beenen, M. A.; Nguyen, S. T.; Scheidt, K. A., *Org. Lett.* **2003**, *5*, 3487.
69. Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H.; Ibata, T., *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1115.
70. (a) Müller, P.; Fruit, C., *Chem. Rev.* **2003**, *103*, 2905. (b) Dauban, P.; Dodd, R. H., *Synlett* **2003**, 1571.
71. (a) Hu, X. E., *Tetrahedron* **2004**, *60*, 2701. (b) Tanner, D., *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
72. Evans, D. A.; Faul, M. M.; Bilodeau, M. T., *J. Am. Chem. Soc.* **1994**, *116*, 2742.
73. Yamada, Y.; Yamamoto, T.; Okawara, M., *Chem. Lett.* **1975**, 361.
74. (a) Li, Z.; Quan, R. W.; Jacobsen, E. N., *J. Am. Chem. Soc.* **1995**, *117*, 5889. (b) Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P. O., *J. Am. Chem. Soc.* **2000**, *122*, 8013.
75. Masse, C. E.; Knight, B. S.; Stavropoulos, P.; Panek, J. S., *J. Am. Chem. Soc.* **1997**, *119*, 6040.
76. Flock, S.; Frauenrath, H., *Synlett* **2001**, 839.
77. (a) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G., *Tetrahedron Lett.* **1997**, *38*, 6897. (b) Dauban, P.; Dodd, R. H., *J. Org. Chem.* **1999**, *64*, 5304. (c) Macikenas, D.; Skrzypczak-Jankun, E.; Protasiewicz, J. D., *J. Am. Chem. Soc.* **1999**, *121*, 7164.
78. Di Chenna, P. H.; Dauban, P.; Ghini, A.; Baggio, R.; Garland, M. T.; Burton, G.; Dodd, R. H., *Tetrahedron* **2003**, *59*, 1009.
79. Dauban, P.; Dodd, R. H., *Org. Lett.* **2000**, *2*, 2327.
80. Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H., *J. Am. Chem. Soc.* **2001**, *123*, 7707.
81. Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M., *J. Am. Chem. Soc.* **1993**, *115*, 5328.
82. Li, Z.; Conser, K. R.; Jacobsen, E. N., *J. Am. Chem. Soc.* **1993**, *115*, 5326.
83. Adam, W.; Roschmann, K. J.; Saha-Möller, C. R., *Eur. J. Org. Chem.* **2000**, 557.
84. (a) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P., *J. Am. Chem. Soc.* **2000**, *122*, 7132. (b) Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P., *J. Org. Chem.* **2002**, *67*, 3450.
85. (a) Ando, T.; Minakata, S.; Ryu, I.; Komatsu, M., *Tetrahedron Lett.* **1998**, *39*, 309. (b) Albone, D. P.; Aujla, P. S.; Taylor, P. C.; Challenger, S.; Derrick, A. M., *J. Org. Chem.* **1998**, *63*, 9569. (c) Chanda, B. M.; Vyas, R.; Bedekar, A. V., *J. Org. Chem.* **2001**, *66*, 30.
86. (a) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B., *J. Am. Chem. Soc.* **1998**, *120*, 6844. (b) Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M., *Angew. Chem., Int. Ed.* **2004**, *43*, 79.
87. (a) Li, G.; Wei, H. X.; Kim, S. H., *Org. Lett.* **2000**, *2*, 2249. (b) Chen, D.; Timmons, C.; Chao, S.; Li, G., *Eur. J. Org. Chem.* **2004**, 3097.
88. Takada, H.; Nishibayashi, Y.; Ohe, K.; Uemura, S.; Baird, C. P.; Sparey, T. J.; Taylor, P. C., *J. Org. Chem.* **1997**, *62*, 6512.
89. Aujla, P. S.; Baird, C. P.; Taylor, P. C.; Mauger, H.; Vallée, Y., *Tetrahedron Lett.* **1997**, *38*, 7453.
90. Takada, H.; Oda, M.; Miyake, Y.; Ohe, K.; Uemura, S., *Chem. Commun.* **1998**, 1557.

91. (a) Müller, J. F. K.; Vogt, P., *Tetrahedron Lett.* **1998**, *39*, 4805. (b) Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M., *Synlett* **2002**, 116. (c) Bolm, C.; Muñiz, K.; Aguilar, N.; Kesselgruber, M.; Raabe, G., *Synthesis* **1999**, 1251.
92. de Vries, A. H. M.; Meetsma, A.; Feringa, B., *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374.
93. Hu, X.; Chen, H.; Zhang, X., *Angew. Chem., Int. Ed.* **1999**, *38*, 3518.
94. Liang, L.; Au-Yeung, T. T. L.; Chan, A. S. C., *Org. Lett.* **2002**, *4*, 3799.
95. Degrado, S. J.; Mizutani, H.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2001**, *123*, 755.
96. Mizutani, H.; Degrado, S. J.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2002**, *124*, 779.
97. Degrado, S. J.; Mizutani, H.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2002**, *124*, 13362.
98. Luchaco-Cullis, C. A.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2002**, *124*, 8192.
99. Hird, A. W.; Hoveyda, A. H., *Angew. Chem., Int. Ed.* **2003**, *42*, 1276.
100. Cesati, R. R.; de Armas, J.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2004**, *126*, 96.
101. Chataigner, I.; Gennari, C.; Ongeri, S.; Piarulli, U.; Ceccarelli, S., *Chem. Eur. J.* **2001**, *7*, 2628.
102. (a) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Aoe, K.; Hiramatsu, H.; Iwata, C., *Tetrahedron* **1996**, *52*, 14177. (b) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Iwata, C., *Tetrahedron:Asymmetry* **1996**, *7*, 993.
103. Ito, H.; Ishizuka, T.; Tateiwa, J.; Sonoda, M.; Hosomi, A., *J. Am. Chem. Soc.* **1998**, *120*, 11196.
104. Clark, C. T.; Lake, J. F.; Scheidt, K. A., *J. Am. Chem. Soc.* **2004**, *126*, 84.
105. Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A., *Tetrahedron Lett.* **2000**, *41*, 6821.
106. Murphy, K. E.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2003**, *125*, 4690.
107. Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C., *Angew. Chem., Int. Ed.* **2003**, *42*, 234.
108. Shi, W. J.; Wang, L. X.; Fu, Y.; Zhu, S. F.; Zhou, Q. L., *Tetrahedron:Asymmetry* **2003**, *14*, 3867.
109. Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K., *J. Org. Chem.* **2003**, *68*, 9723.
110. Wang, C. J.; Shi, M., *J. Org. Chem.* **2003**, *68*, 6229.
111. Boezio, A. A.; Charette, A. B., *J. Am. Chem. Soc.* **2003**, *125*, 1692.
112. Boezio, A. A.; Pytkowicz, J.; Côté A, Charette, A. B., *J. Am. Chem. Soc.* **2003**, *125*, 14260.
113. (a) Wei, C.; Li, C. J., *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Wei, C.; Mague, J. T.; Li, C. J., *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5749.
114. Yao, S.; Fang, X.; Jørgensen, K. A., *Chem. Commun.* **1998**, 2547.
115. Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A., *J. Org. Chem.* **1999**, *64*, 4844.
116. (a) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A., *Angew. Chem., Int. Ed.* **1998**, *38*, 3121. (b) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C., *J. Am. Chem. Soc.* **2004**, *126*, 456.
117. (a) Ley, S. V.; Thomas, A. W., *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Kunz, K.; Scholz, U.; Ganzer D., *Synlett* **2003**, 2428.
118. Marcoux, J. F.; Doye, S.; Buchwald, S. L., *J. Am. Chem. Soc.* **1997**, *119*, 10539.
119. Xing, X.; Padmanaban, D.; Yeh, L. A.; Cuny, G. D., *Tetrahedron* **2002**, *58*, 7903.
120. (a) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L., *Tetrahedron Lett.* **1999**, *40*, 2657. (b) Arterburn, J. B.; Pannala, M.; Gonzalez, A. M., *Tetrahedron Lett.* **2001**, *42*, 1475. (c) Yue, W.; Lewis, S. I.; Koen, Y. M.; Hanzlik, R. P., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1637.
121. Berman, A. M.; Johnson, J. S., *J. Am. Chem. Soc.* **2004**, *126*, 5680.
122. Baskin, J. M.; Wang, Z., *Org. Lett.* **2002**, *4*, 4423.
123. Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A., *Tetrahedron Lett.* **1995**, *36*, 1831.
124. Andrus, M. B.; Chen, X., *Tetrahedron* **1997**, *53*, 16229.
125. Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G., *Tetrahedron Lett.* **1995**, *36*, 2945.
126. Sekar, G.; Datta Gupta, A.; Singh, V. K., *J. Org. Chem.* **1998**, *63*, 2961.
127. Kawasaki, K.; Katsuki, T., *Tetrahedron* **1997**, *53*, 6337.
128. Bayardon, J.; Sinou, D., *J. Org. Chem.* **2004**, *69*, 3121.
129. Schultz, M.; Kluge, R.; Gelalcha, F. G., *Tetrahedron:Asymmetry* **1998**, *9*, 4341.
130. (a) Banerjee, S.; Ghosh, S., *J. Org. Chem.* **2003**, *68*, 3981. (b) Bach, T.; Krüger, C.; Harms, K., *Synthesis* **2000**, 305. (c) Bach, T.; Spiegel, A., *Eur. J. Org. Chem.* **2002**, 645.
131. Langer, K.; Mattay, J.; Heidbreder, A.; Möller, M., *Liebigs Ann. Chem.* **1992**, 257.
132. Bach, T.; Spiegel, A., *Synlett* **2002**, 1305.
133. Sarkar, N.; Nayek, A.; Ghosh, S., *Org. Lett.* **2004**, *6*, 1903.
134. Langer, K.; Mattay, J., *J. Org. Chem.* **1995**, *60*, 7256.

Copper(II) Trifluoromethanesulfonate

$Cu(OSO_2CF_3)_2$

[34946-82-2] $C_2CuF_6O_6S_2$ (MW 361.68)

InChI = 1/2CHF3O3S.Cu/c2*2-1(3,4)8(5,6)7;/h2*(H,5,6,7);/q;;
+2/p-2/f2CF3O3S.Cu/q2*-1;m/rC2CuF6O6S2/c4-1(5,6)
16(10,11)14-3-15-17(12,13)2(7,8)9

InChIKey = SBTSVTLGWRLWOD-YVWFZREUCJ

(dimerization of ketone enolates and TMS enol ethers;[2a,2b] cyclization of dienolates[2c] and unsaturated silyl enol ethers;[4] allylation of ketones;[3] reactions of diazo compounds;[5–10] dehydration of alcohols[11])

Alternate Name: copper(II) triflate.

Physical Data: dec at 530 °C (no definite mp).

Solubility: sol MeOH, EtOH, DMF, MeCN, and formamide; also sol *i*-PrCN and acetone.

Form Supplied in: white powder, commercially available. Blue powder when freshly prepared (see below).

Preparative Methods: most conveniently prepared from copper(II) carbonate and triflic acid (trifluoromethanesulfonic acid) in MeCN.[1] The freshly prepared salt precipitated from Et_2O is pale blue.

Handling, Storage, and Precautions: moisture sensitive; can be handled in air for quick transfers; pure samples are only mildly corrosive. Appears to be indefinitely stable in the absence of air, moisture, and light.

Original Commentary

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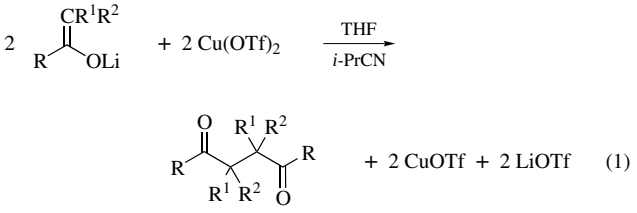
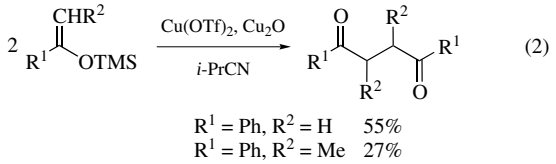
Kent State University, Kent, OH, USA

Oxidative Coupling. Both intermolecular and intramolecular oxidative coupling reactions can be effected using $Cu(OTf)_2$. Examples of dimerization include one-pot syntheses of 1,4-diketones from ketone enolates or from silyl enol ethers (eqs 1 and 2),[2a,2b] and coupling of allylstannanes with TMS-enol ethers

to give γ,δ-unsaturated ketones in good to moderate yields (eq 3). Other copper(II) or tin(IV) catalysts can also be used with allylstannanes. The regiochemistry depends on both the substrate and the catalyst.

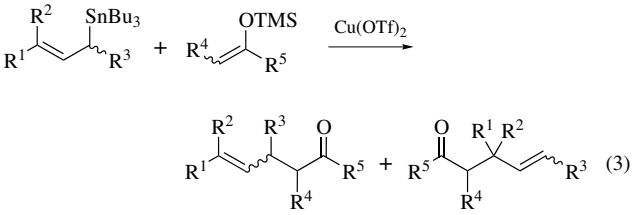


(1)



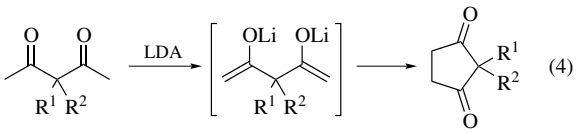
$R^1 = Ph, R^2 = H$ 55%
$R^1 = Ph, R^2 = Me$ 27%

(2)

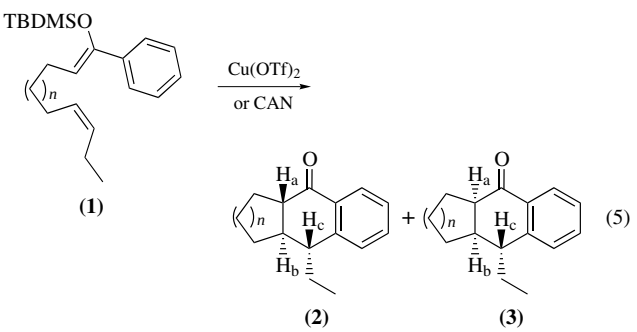


(3)

Examples of intramolecular oxidative cyclizations promoted by $Cu(OTf)_2$ include cyclization of enolates of diketones and diesters (eq 4)[2c] and oxidative cyclization of hydrolytically resistant δ,ε- and ε,ζ-unsaturated silyl enol ethers.[4] For instance, (**1**) reacts with excess $Cu_2O/Cu(OTf)_2$ in MeCN to give a 90% yield of a 20:1 mixture of the *trans*-fused and *cis*-fused tricyclic ketones (**2**) and (**3**) (eq 5).[4]



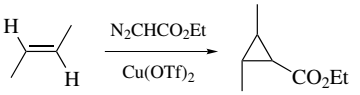
(4)



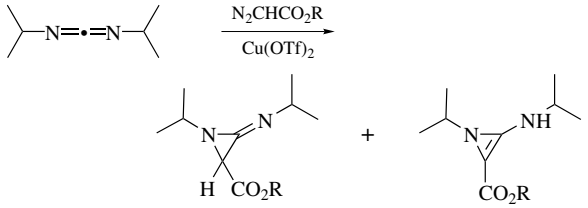
(**1**) (**2**) (**3**)

(5)

Reactions of Diazo Compounds. These include various cyclopropanations where the metal carbenoid generated from the diazoacetic acid esters/$Cu(OTf)_2$ system reacts with alkenes (eq 6) or carbodiimides (eq 7).[5,6]

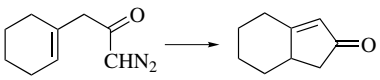


(6)

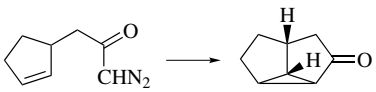


(7)

$Cu(OTf)_2$ is the reagent of choice for intramolecular cyclization of β,γ-unsaturated diazo ketones to cyclopentenones (eq 8) and for intramolecular cyclopropanation of γ,δ-unsaturated diazo ketones (eq 9).[7]

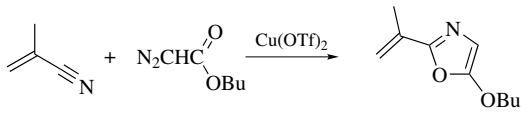


(8)



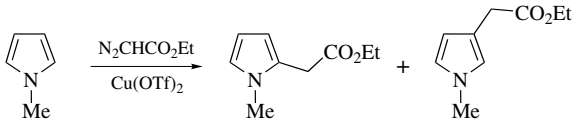
(9)

It is a useful reagent for orthoester homologation via dialkoxycarbenium ions and for oxazole formation by reaction of ketocarbenes (via diazo esters/$Cu(OTf)_2$) with nitriles (eq 10).[8] With unsaturated nitriles, the nitrile group is selectively attacked. Kinetic and ESR evidence shows that $Cu^{II} \rightarrow Cu^{I}$ reduction is the key step.[9]



(10)

The regiochemistry of the monoacetate adducts formed from *N*-methylpyrrole with the carbenoid derived from N_2CHCO_2Et/-$Cu(OTf)_2$ is indicative of a reactive and less discriminating intermediate compared to carbenoids generated from N_2CHCO_2Et with other Cu^{II} reagents (eq 11).[10]

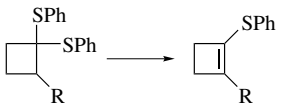


(11)

Angularly functionalized polycyclic systems may be prepared from β,γ-unsaturated diazo ketones by a vinylogous Wolff rearrangement in the presence of copper(II) triflate. Dry copper(II) acetylacetonate is equally suitable.[10]

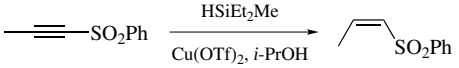
Dehydration of Alcohols. Various tertiary, secondary, and primary alcohols are dehydrated with $Cu(OTf)_2$ to alkenes.[11] Preferred formation of Zaitsev orientation products and (*E*)-alkenes are indicative of a carbocationic mechanism. $Zn(OTf)_2$ and $Mg(OTf)_2$ are ineffective. In selected examples, yields are superior to those of H_2SO_4 and $POCl_3$/pyridine dehydrations.[11]

Elimination Reactions. A $Cu(OTf)_2$/Hünig base combination provides a useful method for converting 1,1-bis(phenylthio)-cyclobutanes to 1-(phenylthio)cyclobutenes (eq 12).[12]



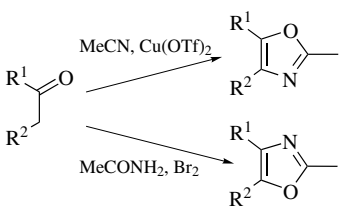
(12)

Reduction of Alkynyl Sulfones. The $HSiEt_2Me/Cu(OTf)_2$ system reduces alkynyl sulfones to *cis* vinylic sulfones (eq 13).[13] The yields with copper(II) tetrafluoroborate are higher than those with $Cu(OTf)_2$. Dimeric side products are formed in some cases.



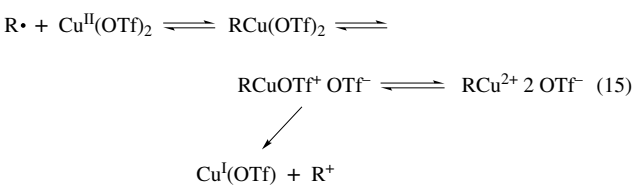
(13)

Oxazoles from Ketones. Aliphatic ketones react with nitriles in the presence of $Cu(OTf)_2$ and catalytic amounts of *p*-toluenesulfonic acid in refluxing MeCN to give oxazoles.[14] The oxazole produced in this way is isomeric with that formed from a ketone and an amide (eq 14).



(14)

Oxidation of Alkyl Radicals. Various alkyl radicals are oxidized with Cu^{II} triflate or perchlorate to carbenium ions whose reactivities are similar to solvolytically formed cations (eq 15).[1] The synthetic utility of such $Cu(OTf)_2$-catalyzed oxidations remains to be explored.



(15)

First Update

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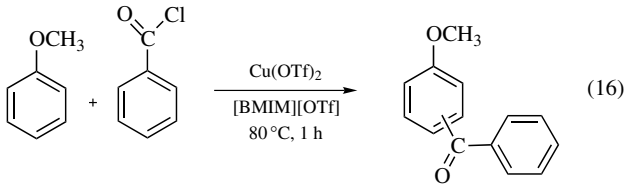
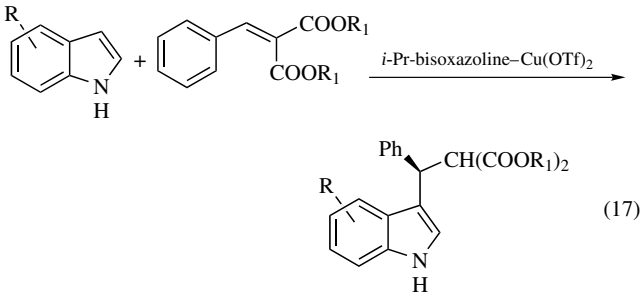
Friedel-Crafts Acylation. Acetylation and benzoylation of aromatics have been performed in ionic liquids such as [BMIM]-$[BF_4]$ by using $Cu(OTf)_2$ as catalyst.[15] Under these conditions, benzoylation of activated aromatics such as anisole (eq 16) is reported to be quantitative and exhibits high *para*-selectivity (*ortho*:*para* = 4:96).



(16)

Friedel-Crafts Alkylation. The ^{i}Pr-bisoxazoline–$Cu(OTf)_2$ system is an efficient catalyst in Friedel-Crafts alkylation of indole (eq 17) with arylidene malonates.[16] Using 10 mol of $Cu(OTf)_2$ in *i*-BuOH, the *S*-enantiomer was obtained in yields ranging from 50 to 94% and with 97% ee (eq 17, R = H, R_1 = Et). The opposite enantiomer was obtained at 0 °C by using CH_2Cl_2 or 1,1,2,2-tetrachloroethane as solvent, in up to 78% ee. The $Cu(OTf)_2$–^{i}Pr-bisoxazoline system also proved to be efficient for the asymmetric Friedel-Crafts reaction of indole derivatives with arylidene malonates.

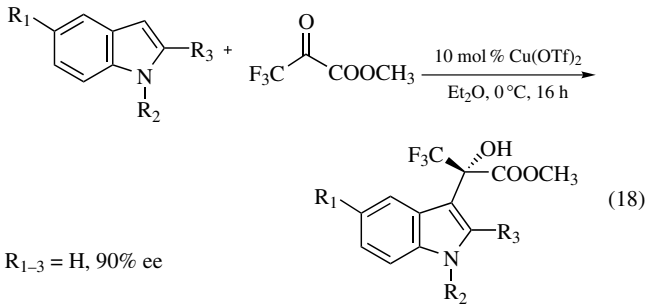


(17)

R = H, 5-Methyl, 5-Methoxy; R_1 = Methyl, Ethyl

Enantioselective Friedel-Crafts Alkylation Reactions. Enantioselective Friedel-Crafts alkylation reactions were performed between substituted indoles and methyl trifluoropyruvate, using a chiral nonracemic C_2-symmetric 2,2′-bipyridyl copper^{II} triflate complex as catalyst.[17] The active copper(II) catalyst was

generated in situ. The corresponding 3,3,3-trifluoro-2-hydroxy-2-indolyl-propionic acid methyl esters were formed in good yield (up to 79%), and in up to 90% enantiomeric excess (eq 18).

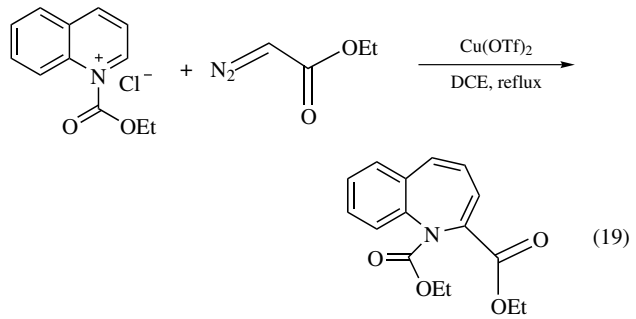


(18)

$R_{1–3}$ = H, 90% ee

In the case of indole itself, the conjugate addition product was formed in excellent yield (97%) and in good enantiomeric excess (59% ee). According to the authors, this was the first report of the use of a chiral nonracemic 2,2′-bipyridyl ligand in catalytic and enantioselective Friedel-Crafts alkylation reactions.

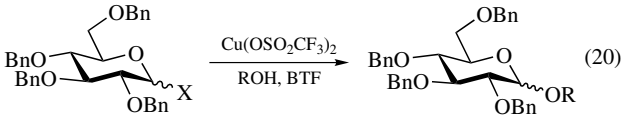
Ring Expansion. An unexpected ring expansion occurred when activated quinoline (eq 19) or isoquinoline was reacted with diazocarbonyl compounds in the presence of 5 mol % of copper(II) trifluoromethanesulfonate.[18]



(19)

The reaction takes place via C–C insertion and leads to novel benzoazepines such as ethyl 1*H*-benzo[*b*]azepine-1-carboxylate and ethyl 3*H*-benzo[*d*]azepine-3-carboxylate, in excellent yields with a high degree of selectivity. Similar results were observed using 10 mol % of $Rh_2(OAc)_4$. It is noteworthy that no reaction was observed with other metal triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$, and $In(OTf)_3$.

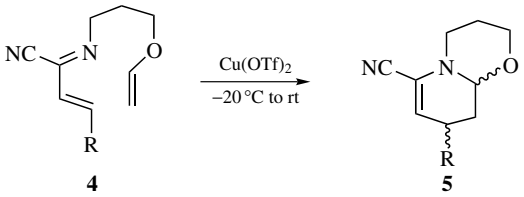
Glycosylation Reactions. Copper(II) trifluoromethanesulfonate acts as catalyst for glycosylation reactions (eq 20) in α,α,α-trifluorotoluene (BTF) solvent, using five different types of glycosyl donors: a glycosyl chloride, a fluoride, a trichloroacetimidate, a 1-*O*-acetyl compound, and a lactol, to give the corresponding glucosides.[19]



(20)

X = Cl, F, OC(=NH)CCl_3, OAc, OH

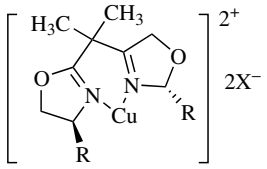
Intramolecular Diels-Alder Reaction of 1-Azadienes. Lewis acids such as $Cu(OTf)_2$, its chiral bisoxazoline complex $Cu(oxaz)_2(OTf)_2$, and $BiCl_3$ catalyze the intramolecular Diels-Alder reaction of 1-azadienes (eq 21). The 2-cyano-1-azadienes (**4**), containing an electron rich enol ether dienophile component, undergo cycloaddition to give the oxazinopiperidines (**5**) in 59–80% yield.[20]



4 **5** (21)

R = H, Me, Ph, OMe

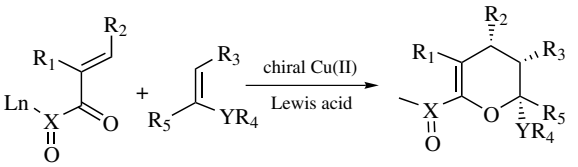
Hetero-Diels-Alder Reactions. The C_2-symmetric bis(oxazoline) Cu(II) complexes (Figure 1) promoted the enantioselective synthesis of dihydropyrans using α,β-unsaturated carbonyl compounds (heterodienes) with electron-rich olefins (heterodienophiles) with high diastereo- and enantioselectivity (eq 22).[21]



X = OTf; SbF_6

R = *t*-Bu; Ph; *i*-Pr; Bn

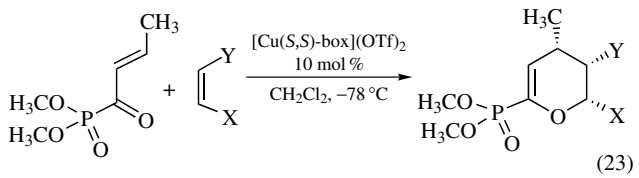
Figure 1



(22)

Cycloadditions can be performed by using 0.2 mol % of the chiral Cu(II) catalyst at room temperature, with selectivities exceeding 90%.

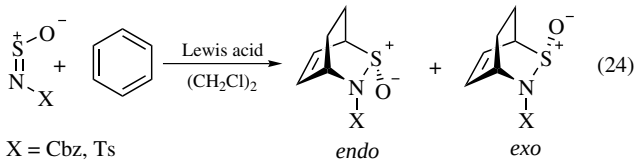
Cycloaddition of crotonyl phosphate with enols gave dihydropyrans in 95% yield (eq 23). The effect of ligand (Ln) and counterion on these reactions were also examined.



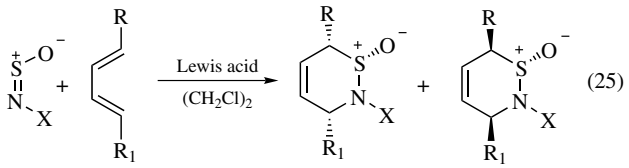
(23)

Asymmetric Hetero-Diels-Alder Reactions. By using stoichiometric amounts of the bis(oxazoline)-copper(II) triflate system as catalyst, asymmetric hetero-Diels-Alder (HDA) cycloaddition reactions were performed with cyclic and acyclic 1,3-dienes.[22] The reported enantioselectivity (70–98% ee) and

yields (60–85%) are satisfactory. Cyclic dienes gave the *endo*-adducts as major products (eq 24), and acyclic dienes gave the *cis*-adducts predominantly (eq 25).



(24)

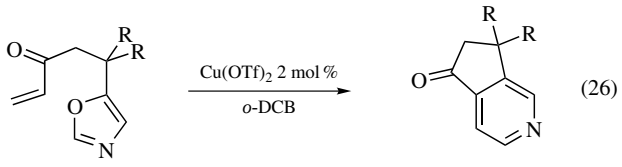


(25)

R, R_1 = H, Me, CH_2OBn

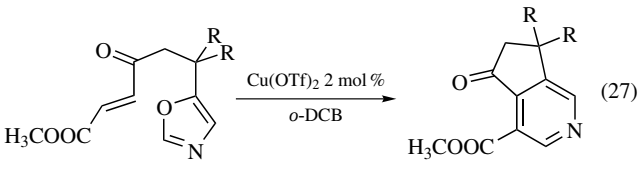
Whereas stereoselective HDA reactions of *N*-sulfinyl dienophiles with 10 mol % $Cu(OTf)_2$ chiral Lewis acid gave poor yields and selectivities, high yields (68–86%) and enantioselectivities (97–98% ee) were achieved in the presence of TMSOTf (100 mol %).

Intramolecular Diels-Alder Reaction of Oxazoles. A catalytic amount of copper(II) triflate promotes the intramolecular Diels-Alder addition of ω-unsaturated oxazoles, as in **6** (eq 26) and **8** (eq 27), to afford the corresponding cyclopenta[*c*]pyridines (**7**) and respectively **9**.[23]



(26)

6 *o*-DCB = *o*-dichlorobenzene **7**
R = CH_3, H

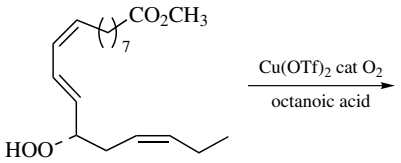


(27)

8 **9**
R = Ch_3, H

By heating **6** (R = CH_3) to 180 °C for 1h, **7** (R = CH_3) was produced in 55% yield; and **9** (R = CH_3) was obtained from **8** (R = CH_3) in 95% yield after 30 min at 150 °C. In the absence of $Cu(OTf)_2$ the yields were 21% and 15%, respectively.

Generation of Peroxy Radicals. Catalytic amounts of $Cu(OTf)_2$ in the presence of octanoic acid under oxygen efficiently convert the methyl (9*Z*,11*E*,15*Z*)-13-hydroperoxyoctadeca-9,11,15-trienone (**10**) into the hydroperoxy dioxolanes (**11**) (eq 28). Methyl (5*Z*,8*Z*,11*Z*,13*E*,15*S*)-15-hydroperoxyeicosa-5,8,11,13-tetraenoate was converted into hydroperoxy bisdioxolanes via an 11-peroxy radical.[24]



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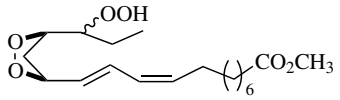
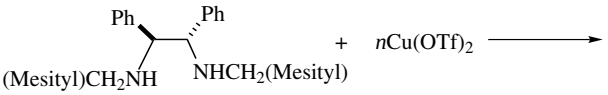


(28)

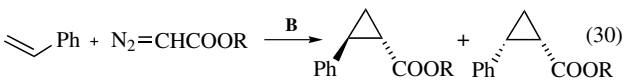
11

Asymmetric Cyclopropanation of Styrene. New chiral copper catalysts **A** or **B** bearing secondary 1,2-diamine ligands (eq 29) were obtained from $Cu(OTf)_2$ (1 mol %), and (1*S*,2*S*)-*N*,*N*′-di(mesitylmethyl)-1,2-diphenyl-1,2-ethanediamine (2–3 mol %), depending upon the molar ratio of ligand to $Cu(OTf)_2$ employed.



Catalysts **A, B** (29)

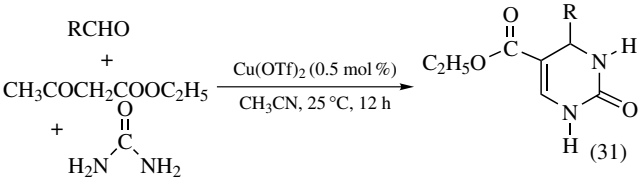
The resulting copper catalysts were utilized in asymmetric cyclopropanations of alkenes (eq 30) with diazo esters in order to effect the decomposition of diazo esters below room temperature.



(30)

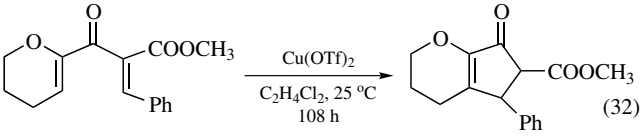
The catalyst **B** was obtained when 2 molar equiv of the ligand were used, and is a colorless diamagnetic complex.[25]

Three-component Condensation Reactions. $Cu(OTf)_2$ catalyzes the three-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (eq 31) in high yields via condensation of aldehydes with keto esters and ureas. For the three-component Biginelli condensation involving benzaldehyde, urea, and ethyl acetoacetate, the reaction proceeds with a low catalyst concentration [0.5 mol % of $Cu(OTf)_2$] at ambient temperature, yielding 3,4-dihydropyrimidin-2(1*H*)-one.[26]



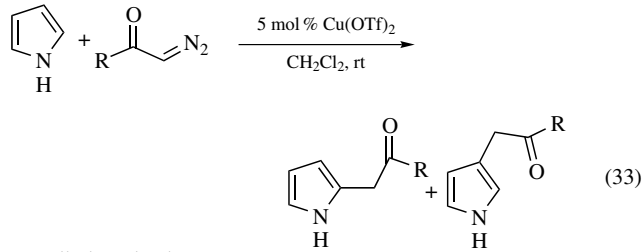
(31)

Nazarov Cyclization. Carbomethoxy divinyl ketones undergo Nazarov cyclization, using $Cu(OTf)_2$ (2 mol %) as catalyst, to give cyclopentenone as a single regio- and stereoisomer.[27]



(32)

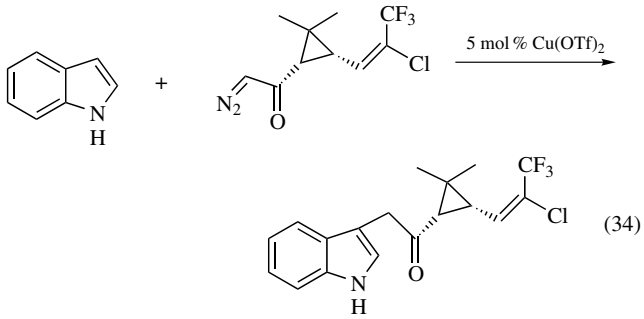
***C*-Alkylation of Pyrroles and Indoles.** Using 10 mol % $InBr_3$ or 5 mol % $Cu(OTf)_2$ as catalyst, pyrroles and indoles were alkylated with diazocarbonyl derivatives (eq 33) via a simple and straightforward method in reasonable yields with good selectivities.[28]



(33)

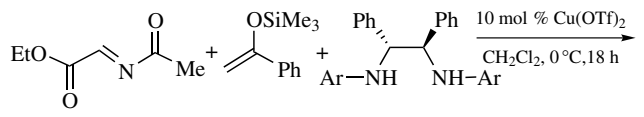
R = alkyl, aryl, ethoxy

Using 10 mol % $InBr_3$, the yield was 58% after 5 h, whereas by employing 5 mol % $Cu(OTf)_2$ the yield was 60% after 3.5 h. Similar results were obtained when indole was reacted with diazocarbonyl derivatives, when the corresponding 3-alkylindole was obtained under mild conditions (eq 34).

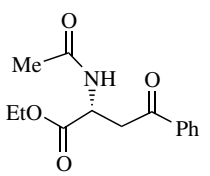


(34)

Mannich-type Reactions. A useful method for the preparation of *N*-acetylated amino acid derivatives was developed using $Cu(OTf)_2$ as catalyst.[29] Thus, a catalytic amount of $Cu(OTf)_2$ and a chiral diamine ligand (10 mol %) catalyzed the reaction between *N*-acylimino esters and silyl enol ethers to afford the corresponding Mannich-type adducts (eq 35) in high yields with high enantioselectivities (80% ee).



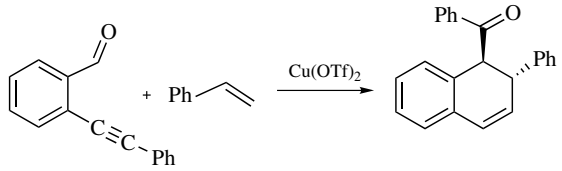
Ar = 1-naphthyl


(35)

85%; 94% ee

This method is useful for the preparation of optically active *N*-acyl aspartic acid derivatives from *N*-acylimino esters and silyl enol ethers.

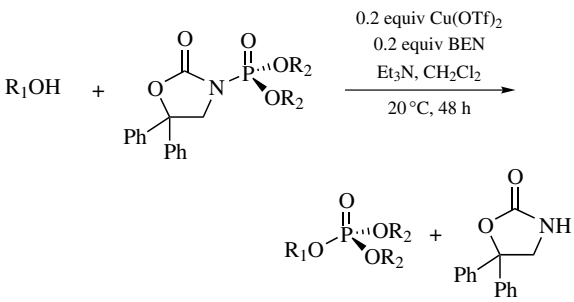
Cycloaddition Reactions. Catalytic amounts of $Cu(OTf)_2$ promoted the [4 + 2] cycloaddition of *o*-alkynyl(oxo)benzenes (eq 36) with alkenes to furnish 1,2-dihydronaphthalene derivatives, bearing an oxo function at the 1-position.[30]



(36)

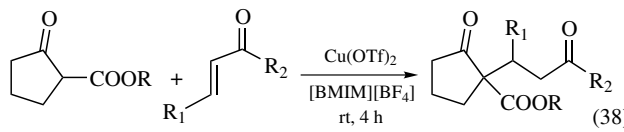
Enantioselective Radical Polymerization. The 2,2′-azo(bis)isobutyronitrile/copper(II) triflate/chiral diamine ligand system was used as an asymmetric reverse atom transfer polymerization initiating system for the enantiomer-selective cyclopolymerization of (2*S*,4*S*/2*R*,4*R*)-2,4-pentanediyl dimethacrylate.[31] Results indicate that the asymmetric reverse ATRP initiating system was effective for the enantioselective radical cyclopolymerization, leading to optically active polymers. Three different chiral diamines were used as ligand including (−)-sparteine.

Phosphorylation of Alcohols with *N*-Phosphoryloxazolidinones. This reaction can be efficiently performed by using copper(II) triflate as catalyst, and the conditions are milder than those employed with alkoxides. Phosphoryl transfer from *N*-phosphoryl 5,5-diphenyl oxazolidone is an important process in synthesis of biomolecules. The optimal ligand is *N*,*N*′-ethylenebis(benzaldimine)(BEN) with 0.2 equiv of $Cu(OTf)_2$ as the best catalyst (eq 37).[32] The ligand-bound Cu^{II} species activates the P=O bond for nucleophilic attack by the alcohol.



(37)

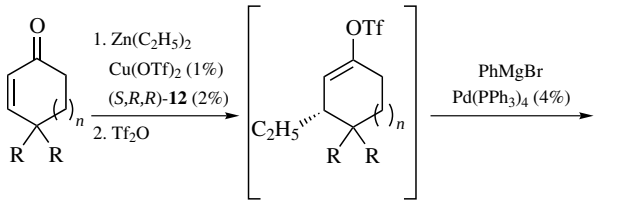
Michael Addition of β-Keto Esters to Unsaturated Carbonyl Compounds. The conjugate addition of β-keto esters to α,β-unsaturated ketones can be effected using 10 mol % copper(II) triflate immobilized in an ionic liquid ([BMIM][BF_4]), as a recyclable catalytic system (eq 38).[33]

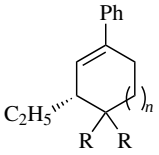


(38)

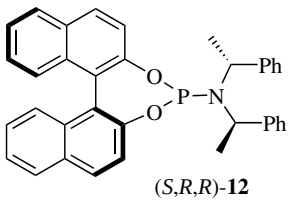
The Michael adducts were obtained in high to quantitative yields, and the products were extracted with diethyl ether. The ionic liquid was washed with ether and reused several times without further purification. The reactivity of $Cu(OTf)_2$ for the condensation of methyl 2-oxocyclopentane-1-carboxylate and methyl vinyl ketone was higher in the ionic liquid solvent than in to conventional solvents. The yields improved from 68% (8 h) in CH_2Cl_2 to 92% (3.5 h) in [BMIM][BF_6].

Asymmetric Conjugate Additions. $Cu(OTf)_2$ in combination with the chiral ligand (**12**) promoted the synthesis of enantiomerically enriched cyclic vinyl triflates directly from cyclic enones in a tandem asymmetric conjugate addition-enolate trapping reaction. Subsequently, the resulting chiral cyclic vinyl triflates were reacted with PhMgBr in the presence of $Pd(PPh_3)_4$ to obtain chiral olefins in good yields and in high enantioselectivity (eq 39).[34] The process represents a one-pot synthesis of chiral olefins.



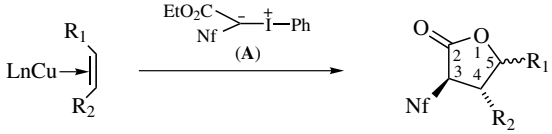


(39)



(*S*,*R*,*R*)-**12**

Synthesis of γ-Lactones. The reaction of phenyliodonio-(ethoxycarbonylnonafluorobutylsulfonyl) methanide (**A**) with alkenes can be performed in the presence of copper(II) triflate, leading to α-nonafluorobutylsulfonyl-γ-lactones in good yields (52–65%).[35] The reaction exhibited high stereoselectivity at C-3 and C-4 (only the *trans*-isomers were found), starting from the sulfonyl ylide (eq 40).



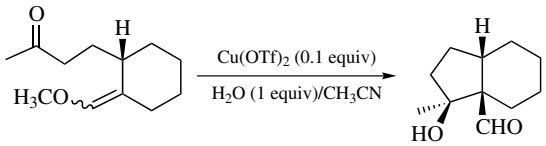
(40)

R_1, R_2 = -CH_3, -C_2H_5, -C_4H_9, -$(CH_2)_n$-; n = 3–5.

Nf = nonafluorobutylsulfonyl

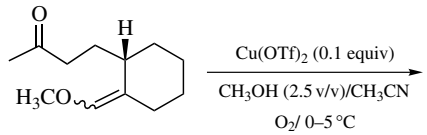
The ylide was prepared by reaction of ethyl (nonafluorobutylsulfonyl)acetate with diacetoxy iodobenzene. Subsequent reaction with alkenes in presence of $Cu(OTf)_2$ afforded the γ-lactones.

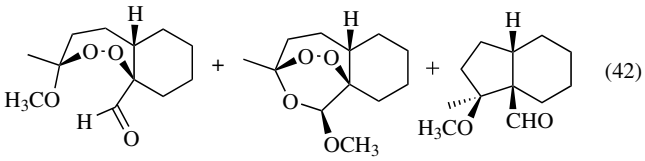
Oxygenation of Aldols. Copper(II) triflate catalyzed the conversion of enol ether (eq 41) into a 2:3 mixture of the *cis*-aldol with no intermediate formation of the corresponding keto aldehyde.[36]



(41)

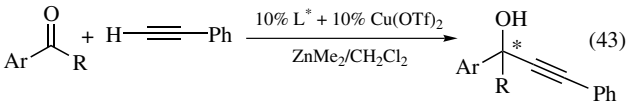
In the presence of oxygen, the aldols were converted into a peracetal and a trioxane (93:7 ratio; 47% combined yield), and the methoxyaldehyde (eq 42) in 12% yield.





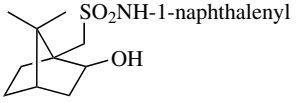
(42)

Alkynylation of Ketones. By combining catalytic amounts of copper(II) triflate and camphorsulfonamides an effective chiral catalyst system is produced, which is effective in the production of tertiary propargylic alcohols, with good to excellent enantioselectivities.[37] These reactions represent a highly enantioselective catalytic addition of alkynyl zinc reagents to simple ketones (eq 43).



(43)

The addition of phenylacetylene to aromatic ketones gave the corresponding tertiary propargylic alcohols. The best enantioselectivity (97% ee) was obtained in alkynylation of 2-chloroacetophenone in the presence of a camphorsulfonamide-based chiral ligand (**13**).



(+)-**13**

Related Reagents. Copper(II) Sulfate; Copper(I) Trifluoromethanesulfonate.

1. Jenkins, C. L.; Kochi, J. K., *J. Am. Chem. Soc.* **1972**, *94*, 843.
2. (a) Kobayashi, Y.; Taguchi, T.; Tokuno, E., *Tetrahedron Lett.* **1977**, 3741. (b) Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E.; Sekiguchi, S., *Chem. Pharm. Bull.* **1980**, *28*, 262. (c) Kobayashi, Y.; Taguchi, T.; Morikawa, T., *Tetrahedron Lett.* **1978**, 3555.

3. Takeda, T.; Ogawa, S.; Koyama, M.; Kato, T.; Fujiwara, T., *Chem. Lett.* **1989**, 1257.
4. Snider, B. B.; Kwon, T., *J. Org. Chem.* **1992**, *57*, 2399.
5. (a) Andrist, A. H.; Agnello, R. M.; Wolfe, D. C., *J. Org. Chem.* **1978**, *43*, 3422. (b) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L., *Organometallics* **1984**, *3*, 44.
6. Hubert, A. J.; Feron, A.; Warin, R.; Teyssie, P., *Tetrahedron Lett.* **1976**, 1317.
7. Doyle, M. P.; Trudell, M. L., *J. Org. Chem.* **1984**, *49*, 1196.
8. Moniotte, Ph. G.; Hubert, A. J.; Teyssie, Ph., *J. Organomet. Chem.* **1975**, *88*, 115.
9. Maryanoff, B. E., *J. Org. Chem.* **1979**, *44*, 4410.
10. Saha, B.; Bhattacharjee, G.; Ghatak, U. R., *Tetrahedron Lett.* **1986**, *27*, 3913.
11. Laali, K.; Gerzina, R. J.; Flajnik, C. M.; Geric, C. M.; Dombroski, A. M., *Helv. Chim. Acta* **1987**, *70*, 607.
12. Kwon, T. W.; Smith, M. B., *Synth. Commun.* **1992**, *22*, 2273.
13. Ryu, I.; Kusumoto, N.; Ogawa, A.; Kambe, N.; Sonoda, N., *Organometallics* **1989**, *8*, 2279.
14. Nagayoshi, K.; Sato, T., *Chem. Lett.* **1983**, 1355.
15. Ross, J.; Xiao, J., *Green Chem.* **2002**, *4*, 129.
16. Zhou, J.; Tang, Y., *Chem. Commun.* **2004**, 432.
17. Lyle, M. P. A.; Draper, N. D.; Wilson, P. D., *Org. Lett.* **2005**, *7*, 901.
18. Yadav, J. S.; Subba Reddy, B. V.; Gupta, M. K.; Prabhakar, A.; Jagadeesh, B., *Chem. Commun.* **2004**, 2124.
19. Yamada, H.; Hayashi, T., *Carbohydr. Res.* **2002**, *337*, 581.
20. Motorina, I. A.; Grierson, D. S., *Tetrahedron Lett.* **1999**, *40*, 7215.
21. Evans, D. A.; Johnson, J. S.; Olhava, E. J., *J. Am. Chem. Soc.* **2000**, *122*, 1635.
22. Bayer, A.; Endeshaw, M. M.; Gautun, O. R., *J. Org. Chem.* **2004**, *69*, 7198.
23. Ohba, M.; Izuta, R., *Heterocycles* **2001**, *55*, 823.
24. Haynes, R. K.; Vonwiller, S. C., *J. Chem. Soc., Chem. Commun.* **1990**, 1102.
25. Kanemasa, S.; Hamura, S.; Harada, E.; Yamamoto, H., *Tetrahedron Lett.* **1994**, *35*, 7985.
26. Paraskar, A. S.; Dewkar, G. K.; Sudalai, A., *Tetrahedron Lett.* **2003**, *44*, 3305.
27. He, W.; Sun, X.; Frontier, A. J., *J. Am. Chem. Soc.* **2003**, *125*, 14278.
28. Yadav, J. S.; Reddy, B. V. S.; Satheesh, G., *Tetrahedron Lett.* **2003**, *44*, 8331.
29. Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M., *J. Am. Chem. Soc.* **2003**, *125*, 2507.
30. Naoki, A.; Taisuke, K.; Yoshinori, Y., *Angew. Chem., Int. Ed.* **2003**, *42*, 3504.
31. Masashi, T.; Ryosuke, S.; Toshifumi, S.; Harumi, K.; Toyoji, K., *Polymer J.* **2003**, *35*, 84.
32. Jones, S.; Smanmoo, C., *Org. Lett.* **2005**, *7*, 3271.
33. Yadav, J. S.; Reddy, B. V.; Baishya, G.; Narsaiah, A. V., *Chem Lett.* **2005**, *34*, 102.
34. Suárez, R. M.; Peña, D.; Minnaard, A. J.; Feringa, B. L., *Org. Biomol. Chem.* **2005**, *3*, 729.
35. Menke, O.; Martinez, A. G.; Subramanian, L. R.; Hanack, M., *Tetrahedron Lett.* **1995**, *36*, 4055.
36. Vonwiller, S. C.; Warner, J. A.; Mann, S. T.; Haynes, R. K., *Tetrahedron Lett.* **1997**, *38*, 2363.
37. Lu, G.; Li, X.; Jia, X.; Chan, A. S., *Angew. Chem., Int. Ed.* **2003**, *44*, 5057.

D

Dibromoborane–Dimethyl Sulfide[1]

$BHBr_2 \cdot SMe_2$

[55671-55-1] $C_2H_7BBr_2S$ (MW 233.77)
InChI = 1/C2H6S.BBr2H/c1-3-2;2-1-3/h1-2H3;1H
InChIKey = PGSRDLGPKTVELT-UHFFFAOYAO

(hydroborating agent providing access to alkyl-[2] and alkenyldibromoboranes[3] and boronic acids[2,4])

Alternate Name: DBBS.
Physical Data: mp 30–35 °C; bp 75 °C/0.1 mmHg.
Solubility: sol dichloromethane, carbon disulfide, carbon tetrachloride.
Form Supplied in: white solid or liquid, 7.8 M in $BHBr_2$.
Preparative Methods: by redistribution of $BH_3{\cdot}SMe_2$ and $BBr_3{\cdot}SMe_2$ or $BH_3{\cdot}SMe_2$ and BBr_3;[5] by the reaction of bromine with $BH_3{\cdot}SMe_2$ in CS_2.[6]
Analysis of Reagent Purity: ^{1}H NMR (CCl_4) δ 2.48, (CS_2) 2.69 ppm; ^{11}B NMR (CCl_4) δ −7.3 (d, J_{B-H} = 160 Hz),[5] (CS_2) −8.2 ppm.[6] Hydrolysis of an aliquot and measuring the hydrogen evolved according to the standard procedure.[7]
Handling, Storage, and Precautions: corrosive liquid; air and moisture sensitive; flammable; stench. Handle and store under nitrogen or argon. Stable indefinitely when stored under nitrogen at 25 °C. Reacts violently with water. This reagent should be handled in a fume hood.

Original Commentary

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Herbert C. Brown
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Hydroboration of Alkenes. Dibromoborane–dimethyl sulfide hydroborates alkenes directly without need for a decomplexing agent (eq 1).[2]

$$RCH{=}CH_2 + BHBr_2 \cdot SMe_2 \xrightarrow[71\text{–}93\%]{CH_2Cl_2} RCH_2CH_2BBr_2 \cdot SMe_2 \quad (1)$$

Regioselectivity of DBBS in the hydroboration of alkenes and derivatives is high, approaching 9-Borabicyclo[3.3.1]nonane, e.g. 1-hexene, styrene, 2-methyl-1-pentene, 2-methyl-2-butene and 4-(dimethylphenylsilyl)-2-pentene, react by placing the boron atom at the less hindered position with ≥99% selectivity.[2,8a] Lower regioselectivity of the hydroboration–oxidation is observed if an excess of alkene is used, due to hydrobromination, which is a side reaction in the hydrolysis–oxidation step.[8b] The reactivity of DBBS toward structurally different alkenes and alkynes is different from that of other hydroborating agents (Table 1).[3,9]

Table 1 Relative reactivity of representative alkynes and alkenes with $BHBr_2 \cdot SMe_2$, 9-BBN, and Sia_2BH

Compound	$BHBr_2 \cdot SMe_2$	9-BBN	Sia_2BH
1-Octene	100	100	100
(*Z*)-3-Hexene	20	0.55	1.25
1-Hexyne	290	15	345
3-Hexyne	5900	0.74	208

Reactions of Alkyldibromoboranes. Alkyldibromoboranes are versatile synthetic intermediates. They are resistant to thermal isomerization, a feature of considerable importance for the regio- and stereoselective synthesis of organoborane intermediates from highly labile alkenic structures.[10]

Standard oxidation of alkyldibromoboranes with alkaline hydrogen peroxide affords alcohols.[2,8b] Conversion of terminal alkenes to carboxylic acids using alkyldibromoboranes works well, although hydrolysis prior to oxidation is needed.[11] Chiral alkyldibromoboranes have been used as catalysts for the asymmetric Diels–Alder reaction.[12,13]

The hydridation–stepwise hydroboration procedure provides a convenient general approach to monoalkylbromoboranes, mixed dialkylbromoboranes, dialkylboranes, totally mixed trialkylboranes, ketones, alcohols (eq 2),[14] and stereodefined alkenes, dienes, and haloalkenes (see below). Mixed alkylalkenylalkynylboranes are also available by this methodology.[15]

$$\text{alkene A} \xrightarrow[CH_2Cl_2]{BHBr_2 \cdot SMe_2} R^ABBr_2 \cdot SMe_2 \xrightarrow[0.25\ LiAlH_4]{\text{alkene B}}$$

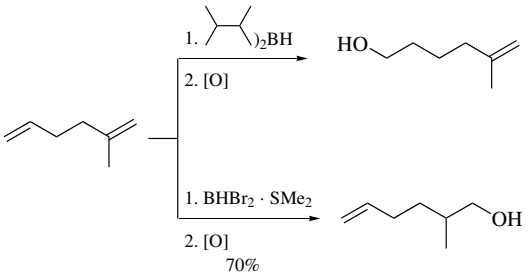
$$R^AR^BBBr \cdot SMe_2 \xrightarrow{MeOH} R^AR^BBOMe \xrightarrow[0.25\ LiAlH_4]{\text{alkene C}} R^AR^BR^CB \quad (2)$$

$$R^AR^BBOMe \xrightarrow[2.\ H_2O_2,\ NaOH]{1.\ Cl_2CHOMe} R^AR^BCO \quad \sim 70\%$$

$$R^AR^BBOMe \xrightarrow[2.\ [O]]{1.\ Cl_2CHOMe} R^AR^BR^CCOH \quad \sim 70\%$$

Hydrolysis and alcoholysis of alkyldibromoboranes provide simple access to alkylboronic acids and esters respectively,[4] which are important synthetic intermediates and reagents for protection of hydroxy groups of diols[16a–f] and derivatizing agents for GC and GC–MS analysis.[16g,h]

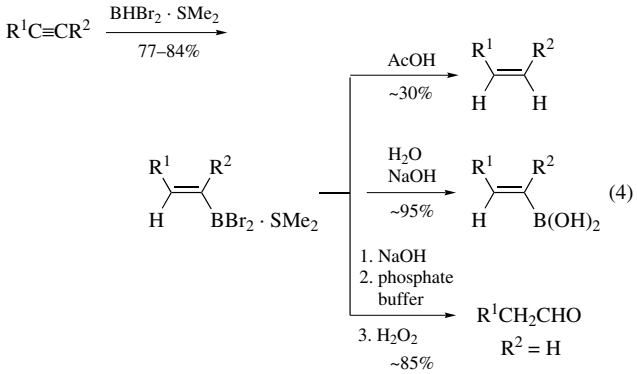
Selective Hydroboration of Dienes and Enynes. The opposite reactivity trends of DBBS and other hydroborating agents makes possible the selective hydroboration of dienes (eq 3)[9] and enynes.[9] In conjugated systems, however, bromoboration of the triple bond is observed.[17]



(3)

Reactions of Alkenyldibromoboranes and Alkenylalkylbromoboranes.

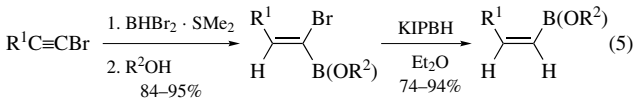
Synthesis of Alkenylboronic Acids, Alkenes, Aldehydes, and Ketones. Alkenyldibromoboranes undergo many of the characteristic reactions of alkenylboranes. The presence of dimethyl sulfide does not interfere in their transformations. Protonolysis with acetic acid in refluxing dichloromethane gives the corresponding alkene. Oxidation leads to aldehydes or ketones (eq 4).[3] Hydrolysis and alcoholysis yields alkenylboronic acids and esters, respectively.



(4)

$R^1 = R^2$ = alkyl; R^1 = alkyl, R^2 = H

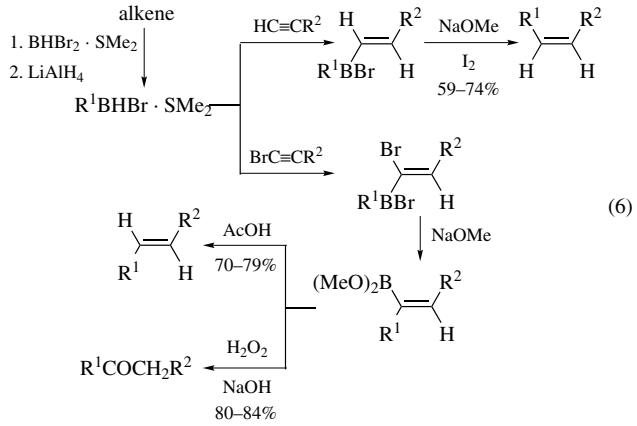
The (*E*)-alkenylboronic acids are directly available from 1-alkynes by hydroboration–hydrolysis (eq 4).[4] The (*Z*)-isomers are prepared from 1-bromo-1-alkynes by hydroboration–hydride reduction (eq 5).[18]



(5)

Synthesis of (E)- and (Z)-Alkenes, Trisubstituted Alkenes, 1,2-Disubstituted Alkenyl Bromides, Ketones, and Enolborates. The synthesis of (*Z*)-alkenes, according to eq 4, is a simple, convenient method, provided the alkynic precursor is readily available. A general Zweifel (*E*)- and (*Z*)-alkene synthesis starts with 1-alkynes and 1-bromo-1-alkynes, respectively. The precursors are hydroborated with monoalkylbromoborane to give the corresponding alkylalkenylbromoboranes. Migration of the alkyl group completes the formation of the carbon skeleton (eq 6).[19–21] The procedure allows full utilization of the alkyl group.

(*Z*)-9-Tricosene (muscalure), the sex pheromone of the housefly (*Musca domestica*), has been prepared by this method in 69% yield and >99% purity.[20,22] Extension of the methodology to trisubstituted alkenes is based on the iodine-induced migration of the second alkyl group R^3 (eq 7).[23]



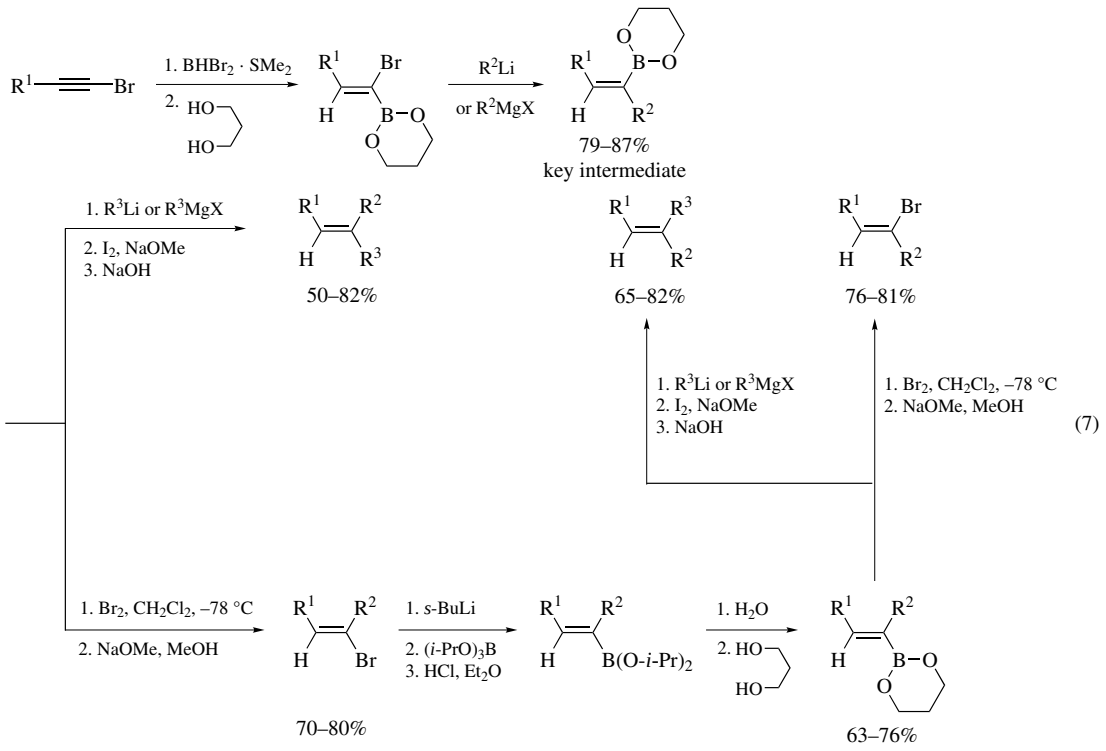
(6)

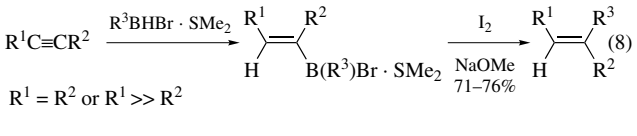
The key alkenylboronate intermediate used for the introduction of the R^3 group (eq 7) is of the same structure as the one shown in eq 6. The procedure works well both for alkyl and aryl R^3 groups. However, a methyl group shows poor migratory aptitude in these reactions.[20,23] If the two *trans*-alkyl groups in the product alkene are the same or differ significantly in steric bulk, an internal alkyne may serve as a starting material (eq 8).[24]

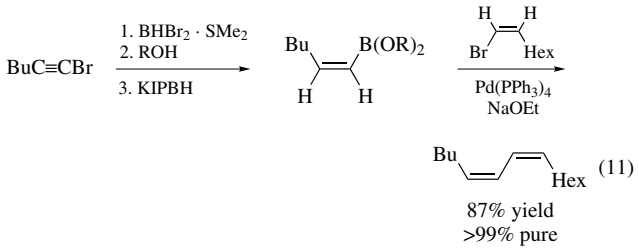
Other approaches to trisubstituted alkenes via organoboranes involve alkynyltrialkyl borates,[25] alkenyltrialkyl borates[26] or the cross-coupling reaction of alkenylboronic acids with alkyl halides.[27] Both (*E*)- and (*Z*)-1,2-disubstituted alkenyl bromides can also be prepared by the methodology shown in eq 7.[28] The boron trifluoride etherate-mediated 1,4-addition of 1,2-disubstituted alkenylboronates affords γ,δ-unsaturated ketones (eq 9).[29] The boronates can also be converted into chiral enolborates for the enantioselective addition to aldehydes.[30]

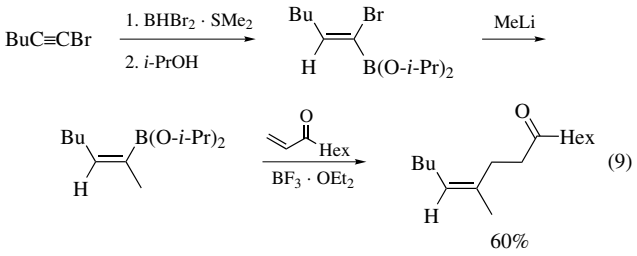
Synthesis of (E)- and (Z)-1-Halo-1-alkenes and α-Bromoacetals. Stereodefined alkenyl halides are important starting materials for the synthesis of alkenyl Grignard[31] and lithium[32] derivatives, pheromones,[33] and (*E,E*)-, (*E,Z*)-, (*Z,E*)- and (*Z,Z*)-dienes by the cross-coupling reaction.[34] An efficient, general (*E*)- and (*Z*)-1-halo-1-alkene synthesis starts with 1-alkynes and 1-halo-1-alkynes respectively, which are converted into the corresponding (*E*)- and (*Z*)-alkenylboronic acids or esters via alkenyldibromoboranes, according to eqs 4 and 5. The alkenylboronic acids and esters react with halogens directly[35–38] or via alkenylmercurials[39] to give the haloalkenes in high stereochemical purity in 70–100% yield (eq 10). In some of these halogenation reactions, alkenyldibromoboranes can be used directly.[35,36] Alternatively, (*Z*)-1-halo-1-alkenes are simply obtained by hydroboration–protonolysis of 1-halo-1-alkynes with 9-BBN or disiamylborane.[40]

Synthesis of Conjugated Dienes. The cross-coupling reaction of alkenylboronates with alkenyl halides is a general method for the synthesis of stereodefined 1,3-dienes (eq 11).[41]

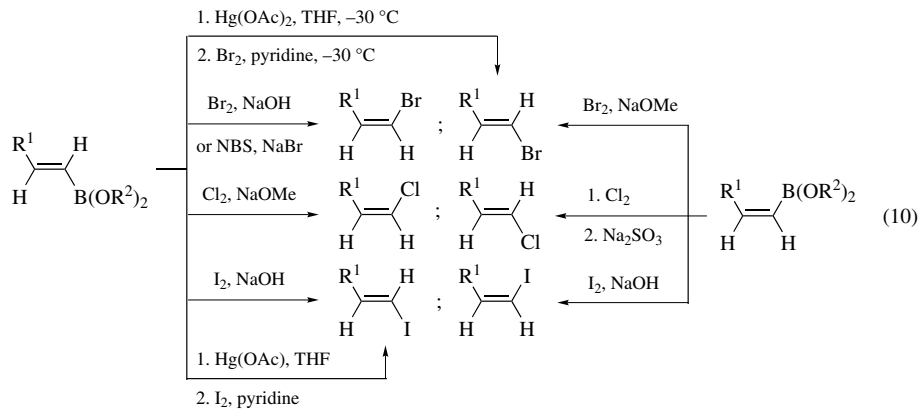








Other Applications. DBBS is an excellent precursor for the formation of bulk powders and ceramic fiber coatings of boron nitride.[42] It has been used for the synthesis of the small carborane *closo*-2,3-$Et_2C_2B_5H_5$,[43] 3-*O*-carboranylcarbene,[44] silver and sodium isocyanoborohydrides,[45] and dications based on the hydrotris(phosphonio)borate skeleton.[46]

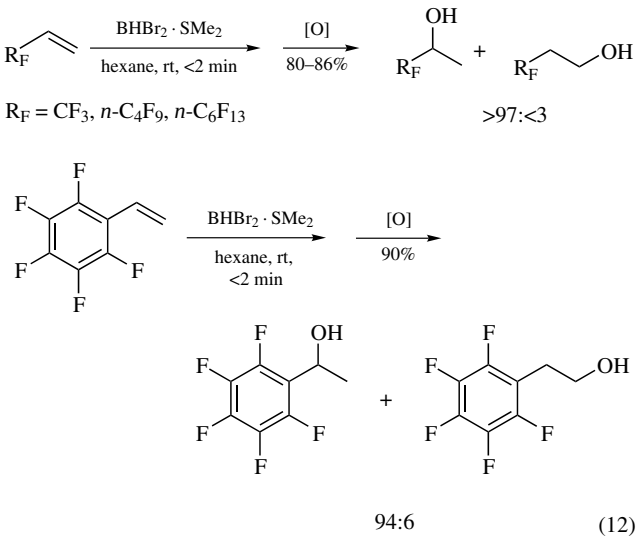


First Update

Chandra D. Roy
EMD Chemicals, Inc., San Diego, CA, USA

Hydroboration of Alkenes and Alkynes.

Hydroboration of Fluoroalkenes. Dibromoborane–dimethyl sulfide (DBBS) has demonstrated to be an excellent hydroborating agent. Based upon kinetic and mechanistic studies, it is clear that the hydroboration reaction exhibits a second-order kinetics (detaching of Me_2S from the boron center follows a dissociative pathway, while the hydroboration process follows an associative mechanism).[47] DBBS hydroborates a wide variety of alkenes and alkynes. Perfluoroalkylethylenes and 2′,3′,4′,5′,6′-pentafluorostyrene undergo Markovnikov hydroboration (>92% regioselectivity) (eq 12).[48]



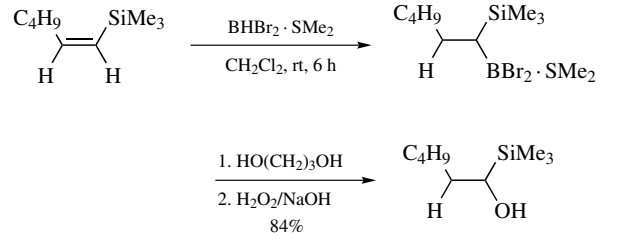
(12)

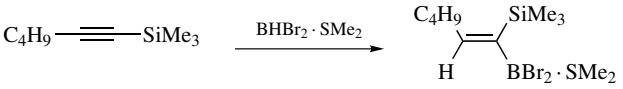
Hydroboration of Silylalkenes and Silylalkynes. (*Z*)-1-Trimethylsilyl-1-alkenes react with DBBS to produce *gem*-dimetalloalkanes, which upon oxidation afford alcohols containing the trimethylsilyl group in high yields (72–84%) (eq 13).[49] Unexpectedly, desilylation of (*Z*)-2-(1-trimethylsilyl-1-hexenyl)dibromoborane is observed during the hydrolysis followed by treatment with 1,3-propanediol.[50]

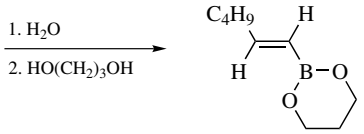
Hydroboration of Organometallic Alkenes. A transition metal compound containing a ligand that combines both an η-arene π-donor group and a boron σ-acceptor (Lewis acid) group has been successfully prepared by the hydroboration of an alkene bearing η-arene derivative of chromium (eq 14).[51]

Reactions of Alkenyldibromoboranes.

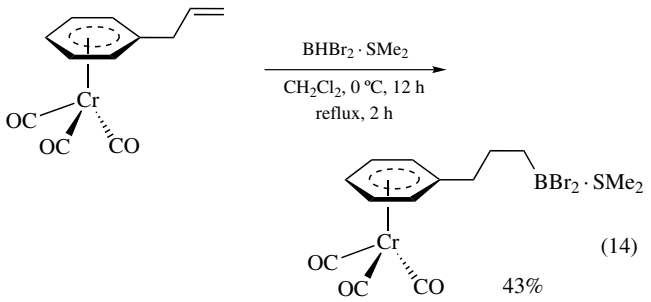
Preparation of 1,1-Bimetallics. Alkenyldibromoboranes are highly promising synthetic intermediates that undergo a host of transformations. An interesting bimetallic compound based on zirconocene and boronic ester is prepared following the hydroboration strategy using $BHBr_2{\cdot}SMe_2$ (eq 15). Optically active 1-alkenylboranes undergo diastereoselective hydrozirconation, which upon treatment with D_2O followed by oxidation provide chiral 1-deuterio primary alcohols (80–93% ee).[52]







(13)

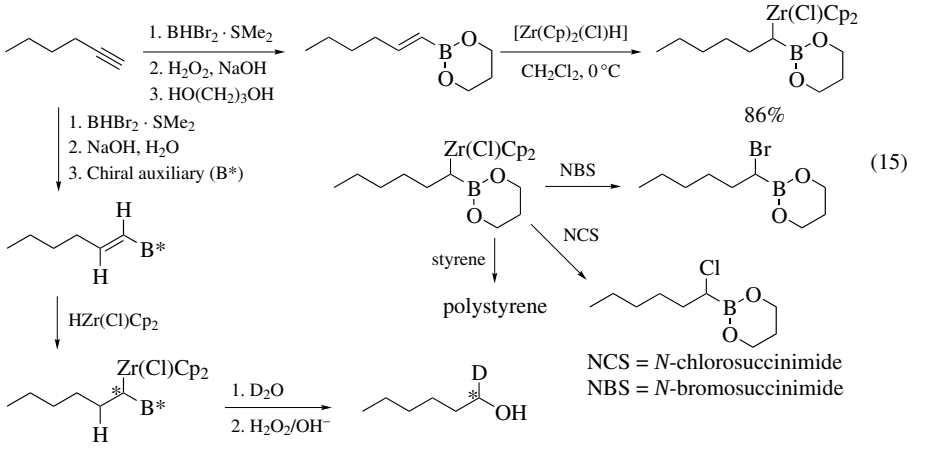


(14)

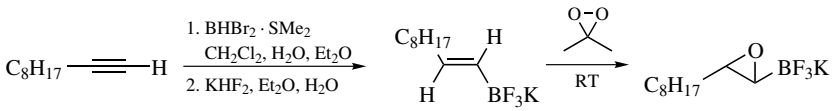
Preparation of Alkenes, Dienes, and Epoxides. Potassium *trans*-1-alkenyltrifluoroborates are very valuable substrates in the Suzuki–Miyaura cross-coupling, which are conveniently prepared in a single pot by the hydroboration of suitable alkynes with DBBS, followed by treatment with KHF_2 in the presence of water.[53] The reactivities possessed by potassium *trans*-1-alkenyltrifluoroborates are complementary to other organoboranes, as demonstrated by permitting olefin epoxidation with dimethyldioxirane with retention of the carbon–boron bond.[54] The synthetic potential of alkenyltrifluoroborates was further explored by synthesizing various trisubstituted conjugated dienes via sequential, stereoselective disubstitution of 1,1-dibromoalkenes utilizing a broad variety of alkenyltrifluoroborates followed by alkyltrifluoroborates in the presence of $Pd[PPh_3]_4$ in a single pot (eq 16).[55]

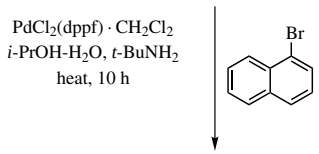
Diastereoselective Synthesis of (Z)- and (E)-Allylsilanes. DBBS has been utilized in the diastereoselective synthesis of (*Z*)- and (*E*)-allylsilanes following a hydroboration–substitution–displacement strategy starting from 1-alkynes (eq 17).[56]

Alkenyldibromoborane as a Dienophile. (1*E*)-Hex-1-en-1-yldibromoborane dimethyl sulfide, obtained by the hydroboration of hex-1-yne with DBBS, reacts with 2,3-dimethylbuta-1,3-diene to provide Diels–Alder adduct that upon methanolysis affords boronic ester in high yield (eq 18).[57]

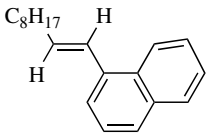


(15)

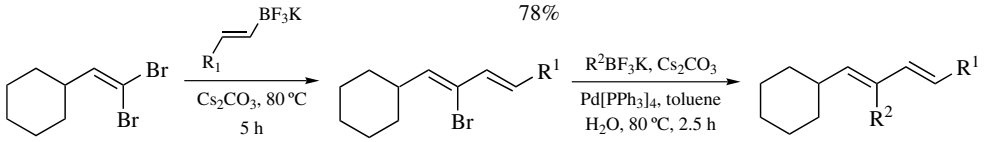




(16)

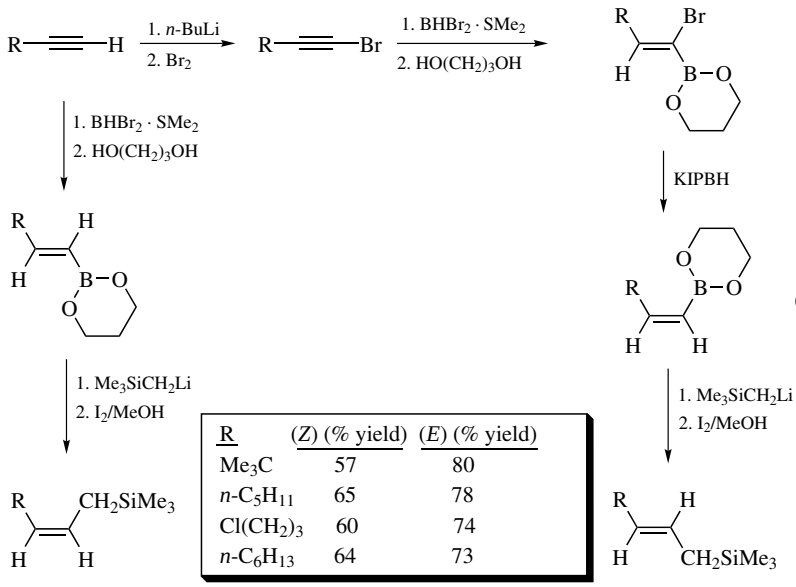


78%



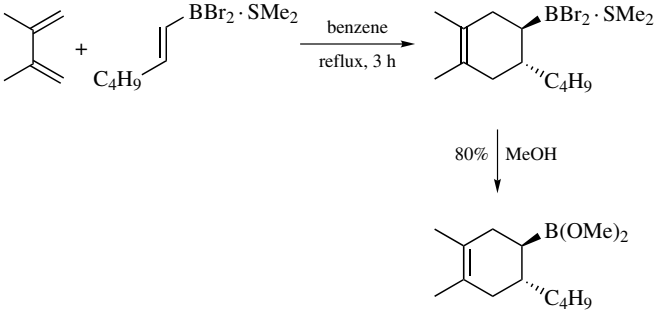
R^1 = C_8H_{17}, $NC(CH_2)_3$, $Cl(CH_2)_3$, $PhCH_2CH_2$

R^2 = $PivO(CH_2)_4BF_3K$

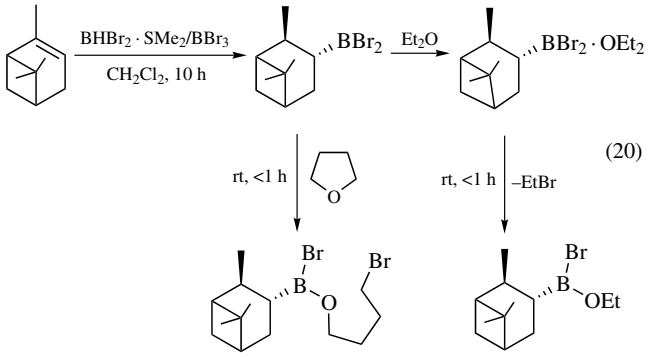


(17)

R	(*Z*) (% yield)	(*E*) (% yield)
Me_3C	57	80
n-C_5H_{11}	65	78
$Cl(CH_2)_3$	60	74
n-C_6H_{13}	64	73



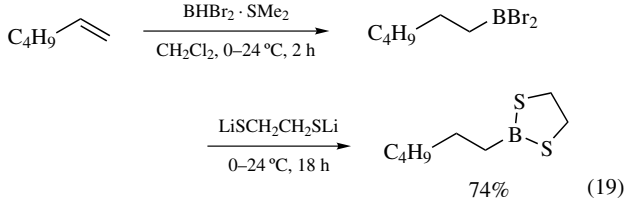
(18)



(20)

Reactions of Alkyldibromoboranes.

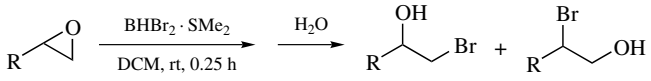
Reaction with Ethane-1,2-dithiol Lithium Salt. Dithiaborolanes can also be prepared in good yields by the reaction of alkyldibromoboranes with lithium salt of ethane-1,2-dithiol (eq 19).[58]



(19)

Reactions with Ethers and Furans. *B,B*-Dibromoisopinocampheylborane (IpcBBr$_2$), prepared by the hydroboration of α-pinene with DBBS in the presence of BBr$_3$, very effectively cleaves diethyl ether and tetrahydrofuran in <2 h (eq 20).[59]

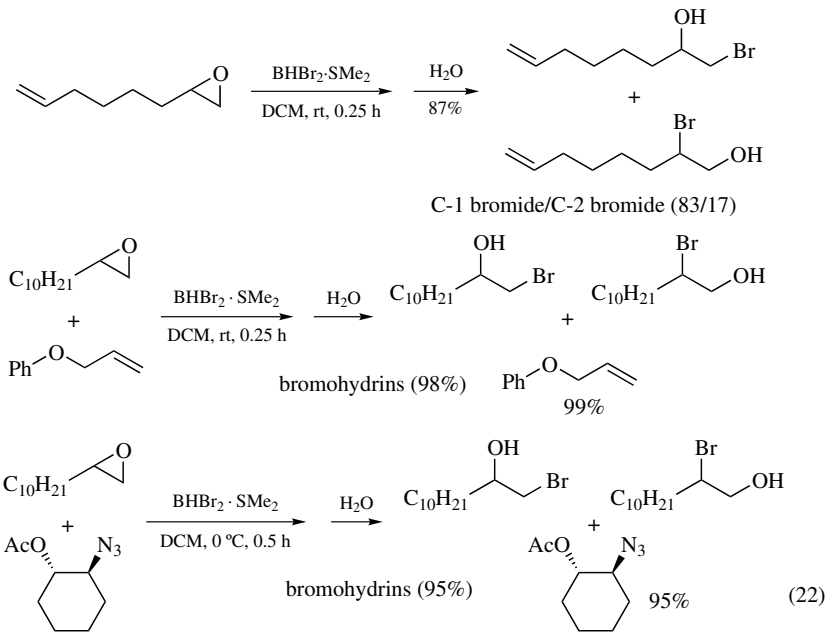
Regio- and Chemoselective Halogenative Cleavage of Epoxides. DBBS very efficiently and regioselectively cleaves terminal epoxides into 1,2-bromohydrins in 15 min in CH_2Cl_2 (eq 21). With the exception of styrene oxide, the transfer of bromine takes place at the less hindered carbon (terminal carbon). In the case of styrene oxide, the bromine is transferred at benzylic position.[60]



R	RCH(OH)CH$_2$Br/RCH(Br)CH$_2$OH	Yield (%)
$C_{10}H_{21}$	90/10	90
$PhCH_2$	89/11	95
Ph	07/93	83

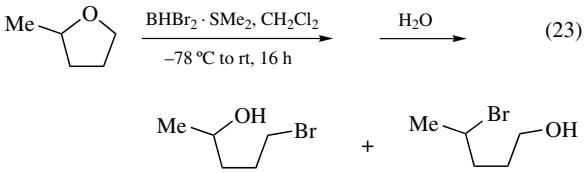
(21)

The preferential reactivity of DBBS toward the epoxy moiety in the presence of other reactive functional groups, such as alkene, alkyne, allene, allyl ether, acetal, ketal, aldehyde, ketone, azide, ester, and nitrile, clearly displays excellent chemoselectivity (eq 22).[60]



(22)

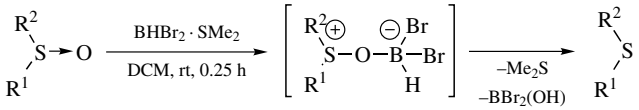
Regiocontrolled Opening of 2-Methyltetrahydrofuran. The cleavage of 2-methyltetrahydrofuran with DBBS provides a mixture of regioisomeric bromohydrins (88%), 1-bromopentan-4-ol and 4-bromopentan-1-ol (72:28) (eq 23).[61]



(23)

total yield: 88%
C-1 bromide:C-2 bromide (72:28)

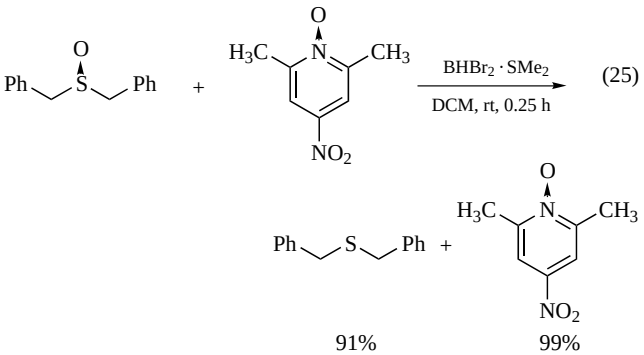
Chemoselective Deoxygenation of Sulfoxides. DBBS is an exceptionally effective reagent for the rapid deoxygenation of sulfoxides to sulfides. Aliphatic and aromatic sulfoxides undergo deoxygenation in <15 min at room temperature in CH_2Cl_2 to afford sulfides in excellent chemical yields (eq 24).[62]



R^1	R^2	Yield (%)
C_4H_9	C_4H_9	90
Ph	CH_3	92
Ph	Ph	90

(24)

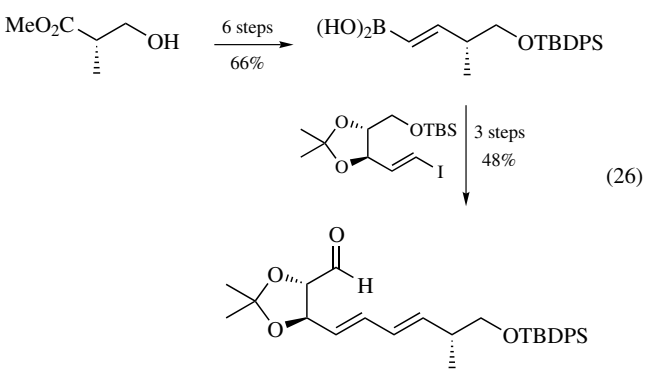
The chemoselectivity of DBBS is demonstrated by reacting dibenzyl sulfoxide in the presence of other functional groups, such as alkene, azide, ketone, azide, and *N*-oxide (eq 25).



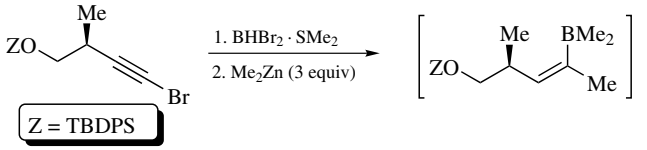
(25)

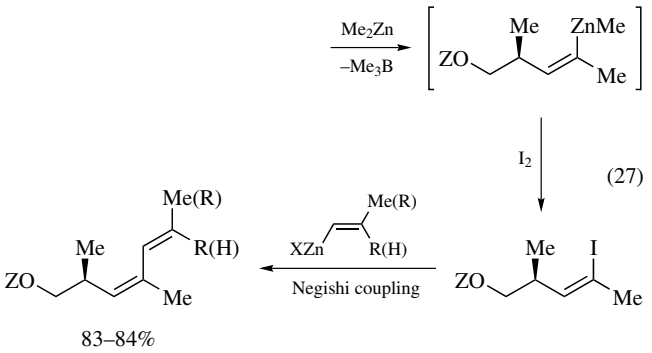
Applications of DBBS in Natural Products Synthesis. A key fragment of (−)-amphidinolide E is synthesized from TBDPS ether of methyl (*S*)-3-hydroxy-2-methylpropanoate through reduction, oxidation, Corey–Fuchs homologation, hydroboration–hydrolysis (utilizing DBBS), Suzuki coupling, deprotection, and oxidation (eq 26).[63]

Highly synthetically demanding (*Z*)-trisubstituted alkenes and their derivatives (useful advanced intermediates for archazolid A and B, (+)-discodermolide and (−)-callystatin A) are prepared from 1-haloalkyne via hydroboration–migratory insertion–Zn-promoted iodinolysis–Pd-catalyzed organozinc cross-coupling (eq 27).[64]



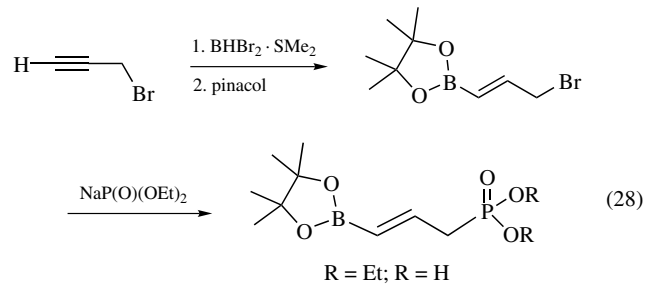
(26)





(27)

Phosphonoboronates are highly promising MMP-2 protease inhibitors that have been conveniently synthesized by hydroboration of propargyl bromide with DBBS followed by Michaelis–Becker reaction (eq 28).[65]

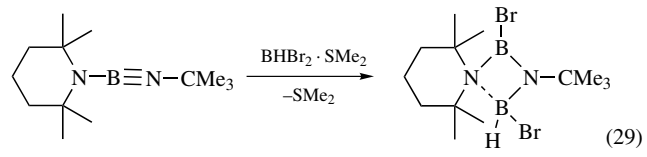


(28)

R = Et; R = H

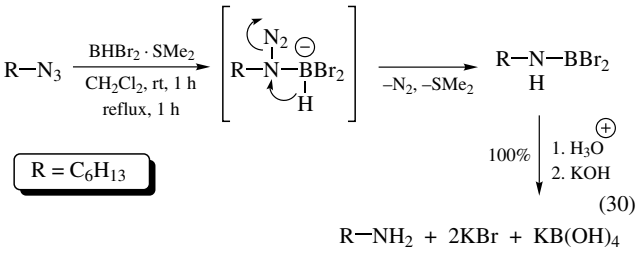
Miscellaneous Reactions.

Haloboration of Boron–Nitrogen Triple Bond. DBBS exclusively reacts with (*tert*-butylimino)(2,2,6,6-tetramethylpiperidino)borane to yield a cyclic haloborated product (eq 29).[66]



(29)

Reduction of Azide. DBBS very effectively and quantitatively reduces *n*-hexylazide into *n*-hexylamine in 2–3 h in dichloromethane (eq 30).[67]



(30)

Other Applications. DBBS has been used for the synthesis of boronic acid-based calix[6]arene) (acts as a single-chain surfactant at the air–water interface),[68] 14-vertex carborane,[69] and 14-vertex metallocarborane,[70] 14- and 15-vertex ruthenacarboranes,[71] and organo-tricyanoborates as tectons.[72]

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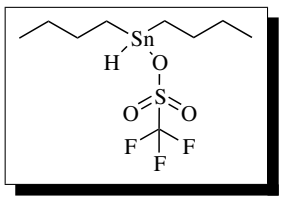
Related Reagents. Dichloroborane–Dimethyl Sulfide.

1. (a) Brown, H. C.; Zaidlewicz, M., *Pol. J. Appl. Chem.* **1982**, *26*, 155. (b) Brown, H. C.; Kulkarni, S. U., *J. Organomet. Chem.* **1982**, *239*, 23. (c) Pelter, A.; Smith, K., *Comprehensive Organic Synthesis* **1991**, *8*, 703.
2. Brown, H. C.; Ravindran, N.; Kulkarni, S. U., *J. Org. Chem.* **1980**, *45*, 384.
3. Brown, H. C.; Campbell, J. B., Jr., *J. Org. Chem.* **1980**, *45*, 389.
4. Brown, H. C.; Bhat, N. G.; Somayaji, V., *Organometallics* **1983**, *2*, 1311.
5. Brown, H. C.; Ravindran, N., *Inorg. Chem.* **1977**, *16*, 2938.
6. Kingberger, K.; Siebert, W., *Z. Naturforsch., Teil B* **1975**, *30*, 55.
7. Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975, p 239.
8. (a) Fleming, I.; Lawrance, N. J., *J. Chem. Soc., Perkin Trans. 1* **1992**, 3309. (b) Brown, H. C.; Racherla, U. S., *J. Org. Chem.* **1986**, *51*, 895.
9. Brown, H. C.; Chandrasekharan, J., *J. Org. Chem.* **1983**, *48*, 644.
10. Brown, H. C.; Racherla, U. S., *J. Org. Chem.* **1983**, *48*, 1389.
11. Brown, H. C.; Kulkarni, S. V.; Khanna, V. V.; Patil, V. D.; Racherla, U. S., *J. Org. Chem.* **1992**, *57*, 6173.
12. (a) Bir, G.; Kaufmann, D., *Tetrahedron Lett.* **1987**, *28*, 777. (b) *J. Organomet. Chem.* **1990**, *390*, 1.
13. Kaufmann, D.; Boese, R., *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545.
14. Kulkarni, S. U.; Basavaiah, D.; Zaidlewicz, M.; Brown, H. C., *Organometallics* **1982**, *1*, 212.
15. Brown, H. C.; Basavaiah, D.; Bhat, N. G., *Organometallics* **1983**, *2*, 1468.
16. (a) Reese, C. B. In *Protective Groups in Organic Chemistry*; McOmie, J. F. W., Ed., Plenum: New York, 1973, p 135. (b) Garlaschelli, L.; Mellerio, G.; Vidari, G., *Tetrahedron Lett.* **1989**, *30*, 597. (c) Dahlhoff, W. V.; Köster, R., *Heterocycles* **1982**, *18*, 421. (d) *J. Org. Chem.* **1977**, *42*, 3151. (e) Wiecko, J.; Sherman, W. R., *J. Am. Chem. Soc.* **1976**, *98*, 7631. (f) Fréchet, J. M. J.; Nuyens, L. J.; Seymour, E., *J. Am. Chem. Soc.* **1979**, *101*, 432. (g) Knapp, D. R. *Handbook of Analytical Derivatization Reactions*; Wiley: New York, 1979. (h) Schurig, V.; Wistuba, D., *Tetrahedron Lett.* **1984**, *25*, 5633.
17. Rowley, E. G.; Schore, N. E., *J. Org. Chem.* **1992**, *57*, 6853.
18. Brown, H. C.; Imai, T., *Organometallics* **1984**, *3*, 1392.
19. Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Lee, H. D.; Negishi, E.; Katz, J. J., *J. Org. Chem.* **1986**, *51*, 5270.
20. Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Bhat, N. G.; Vara Prasad, J. V. N., *J. Org. Chem.* **1988**, *53*, 239.
21. Brown, H. C.; Imai, T.; Bhat, N. G., *J. Org. Chem.* **1986**, *51*, 5277.
22. Brown, H. C.; Basavaiah, D., *J. Org. Chem.* **1982**, *47*, 3806.
23. Brown, H. C.; Bhat, N. G., *J. Org. Chem.* **1988**, *53*, 6009.
24. Brown, H. C.; Basavaiah, D., *J. Org. Chem.* **1982**, *47*, 5407.
25. (a) Pelter, A.; Bentley, T. W.; Harrison, C. R.; Subrahmanyam, C.; Laub, R. J., *J. Chem. Soc., Perkin Trans. 1* **1976**, 2419. (b) Pelter, A.; Gould, K. J.; Harrison, C. R., *J. Chem. Soc., Perkin Trans. 1* **1976**, 2428. (c) Pelter, A.; Harrison, C. R.; Subrahmanyam, C.; Kirkpatrick, D., *J. Chem. Soc., Perkin Trans. 1* **1976**, 2435. (d) Pelter, A.; Subrahmanyam, C.; Laub, R. J.; Gould, K. J.; Harrison, C. R., *Tetrahedron Lett.* **1975**, 1633.
26. (a) LaLima, N. J., Jr.; Levy, A. B., *J. Org. Chem.* **1978**, *43*, 1279. (b) Levy, A. B.; Angelastro, R.; Marinelli, E. R., *Synthesis* **1980**, 945.
27. (a) Satoh, M.; Miyaura, N.; Suzuki, A., *Chem. Lett.* **1986**, 1329. (b) Satoh, Y.; Serizawa, H.; Miyaura, N.; Hara, S.; Suzuki, A., *Tetrahedron Lett.* **1988**, *29*, 1811.
28. (a) Brown, H. C.; Bhat, N. G., *Tetrahedron Lett.* **1988**, *29*, 21. (b) Brown, H. C.; Bhat, N. G.; Rajagopalan, S., *Synthesis* **1986**, 480.
29. Hara, S.; Hyuga, S.; Aoyama, M.; Sato, M.; Suzuki, A., *Tetrahedron Lett.* **1990**, *31*, 247.
30. Basile, T.; Biondi, S.; Boldrini, G. P.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A., *J. Chem. Soc., Perkin Trans. 1* **1989**, 1025.
31. Normant, H., *Adv. Org. Chem.* **1960**, *2*, 1.
32. Dreiding, A. S.; Pratt, R. J., *J. Am. Chem. Soc.* **1954**, *76*, 1902.
33. (a) Rossi, R.; Carpita, A.; Quirici, M. G., *Tetrahedron* **1981**, *37*, 2617. (b) Rossi, R.; Carpita, A.; Quirici, M. G.; Gaudenzi, L., *Tetrahedron* **1982**, *38*, 631.
34. (a) Miyaura, N.; Suginome, H.; Suzuki, A., *Tetrahedron Lett.* **1983**, *24*, 1527. (b) Suzuki, A., *Pure Appl. Chem.* **1991**, *63*, 419. (c) Cassani, G.; Massardo, P.; Piccardi, P., *Tetrahedron Lett.* **1982**, *24*, 2513.
35. Brown, H. C.; Subrahmanyam, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. G., *J. Org. Chem.* **1989**, *54*, 6068.
36. Brown, H. C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. G., *J. Org. Chem.* **1989**, *54*, 6075.
37. (a) Brown, H. C.; Somayaji, V., *Synthesis* **1984**, 919. (b) Brown, H. C.; Hamaoka, T.; Ravindran, N., *J. Am. Chem. Soc.* **1973**, *95*, 5786.
38. (a) Kabalka, G. W.; Sastry, K. A. R.; Knapp, F. F.; Srivastava, P. C., *Synth. Commun.* **1983**, *13*, 1027. (b) Kabalka, G. W.; Sastry, K. A. R.; Somayaji, V., *Heterocycles* **1982**, *18*, 157. (c) Kunda, S. A.; Smith, T. L.; Hylarides, M. D.; Kabalka, G. W., *Tetrahedron Lett.* **1985**, *26*, 279.
39. Brown, H. C.; Larock, R. C.; Gupta, S. K.; Rajagopalan, S.; Bhat, N. G., *J. Org. Chem.* **1989**, *54*, 6079.
40. Brown, H. C.; Blue, C. D.; Nelson, D. J.; Bhat, N. G., *J. Org. Chem.* **1989**, *54*, 6064.
41. Miyaura, N.; Satoh, M.; Suzuki, A., *Tetrahedron Lett.* **1986**, *27*, 3745.
42. Beck, J. S.; Albani, C. R.; McGhie, A. R.; Rothman, J. C.; Sneddon, L. G., *Chem. Mater.* **1989**, *1*, 433.
43. Beck, J. S.; Sneddon, L. G., *Inorg. Chem.* **1990**, *29*, 295.
44. Li, J.; Caparrelli, D. J.; Jones, Jr. M., *J. Am. Chem. Soc.* **1993**, *115*, 408.
45. Györi, B.; Emri, J.; Fehér, I., *J. Organomet. Chem.* **1983**, *255*, 17.
46. (a) Schmidbaur, H.; Wimmer, T.; Reber, G.; Müller, G., *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1071. (b) Schmidbaur, H.; Wimmer, T.; Grohmann, A.; Steigelman, O.; Müller, G., *Chem. Ber.* **1989**, *122*, 1607.
47. (a) Jaganyi, D.; Xaba, N.; Mzinyati, A.; Grimmer, C., *J. Organomet. Chem.* **2007**, *692*, 1150. (b) Xaba, N.; Jaganyi, D., *J. Organomet. Chem.* **2007**, *692*, 4052.
48. Brown, H. C.; Chen, G.-M.; Jennings, M. P.; Ramachandran, P. V., *Angew. Chem., Int. Ed.* **1999**, *38*, 2052.
49. Bhat, N. G.; Garza, A., *Tetrahedron Lett.* **2003**, *44*, 6833.

50. Bhat, N. G.; Aguirre, C. P., *Tetrahedron Lett.* **2000**, *41*, 8027.
51. Green, M. L. H.; Wagner, M., *J. Chem. Soc., Dalton Trans.* **1996**, 2467.
52. (a) Skrzypczak-Jankun, E.; Cheesman, B. V.; Zheng, Bin.; Lemert, R. M.; Asthana, S.; Srebnik, M., *J. Chem. Soc., Chem. Commun.* **1994**, 127. (b) Zhang, B.; Srebnik, M., *Tetrahedron Lett.* **1994**, *35*, 6247.
53. Molander, G. A.; Bernardi, C. R., *J. Org. Chem.* **2002**, *67*, 8424.
54. Molander, G. A.; Ribagorda, M., *J. Am. Chem. Soc.* **2003**, *125*, 11148.
55. Molander, G. A.; Yokoyama, Y., *J. Org. Chem.* **2006**, *71*, 2493.
56. Bhat, N. G.; Lai, W. C.; Carroll, M. B., *Tetrahedron Lett.* **2007**, *48*, 4267.
57. Noiret, N.; Youssofi, A.; Carboni, B.; Vaultier, *J. Chem. Soc., Chem. Commun.* **1992**, 1105.
58. Stoddard, J. M.; Shea, K. J., *Chem. Commun.* **2004**, 830.
59. Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J., *Heteroatom Chem.* **1995**, *6*, 117.
60. (a) Roy, C. D.; Brown, H. C., *J. Organament. Chem.* **2007**, *692*, 1608. (b) Brown, H. C.; Roy, C. D., *Molecules Online* **1998**, *2*, 114.
61. Roy, C. D., *Aust. J. Chem.* **2006**, *59*, 657.
62. Roy, C. D.; Brown, H. C., *J. Chem. Res.* **2006**, 642.
63. Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E., *Angew. Chem., Int. Ed.* **2006**, *45*, 8019.
64. Negishi, E.; Huang, Z., *J. Am. Chem. Soc.* **2007**, *129*, 14788.
65. Pergament, I.; Reich, R.; Srebnik, M., *Bioory Med. Chem. Lett.* **2002**, *12*, 1215.
66. Braun, U.; Böck, B.; Nöth, H.; Schwab, I.; Schwartz, M.; Weber, S.; Wietelmann, U., *Eur. J. Inorg. Chem.* **2004**, 3612.
67. Salunkhe, A. M.; Ramachandran, P. V.; Brown, H. C., *Tetrahedron* **2002**, *58*, 10059.
68. Hendel, R. A.; Janout, V.; Lee, W.; Regen, S. L., *Langmuir* **1996**, *12*, 5745.
69. Deng, L.; Chan, H.-S.; Xie, Z., *Angew. Chem., Int. Ed.* **2005**, *44*, 2128.
70. (a) Deng, L.; Chan, H.-S.; Xie, Z., *J. Am. Chem. Soc.* **2006**, *128*, 5219. (b) Zhang, J.; Deng, L.; Chan, H.-S.; Xie, Z., *J. Am. Chem. Soc.* **2007**, *129*, 18.
71. Deng, L.; Zhang, J.; Chan, H.-S.; Xie, Z., *Angew. Chem., Int. Ed.* **2006**, *45*, 4309.
72. Yao, H.; Kuhlman, M. L.; Rauchfuss, T. B.; Wilson, S. R., *Inorg. Chem.* **2005**, *44*, 6256.

Dibutyl(trifluoromethanesulfoxy)stannane



[847205-17-8] $C_9H_{19}F_3O_3SSn$ (MW 383.00)

InChI = 1/2C4H9.CHF3O3S.Sn.H/c2*1-3-4-2;2-1(3,4)8(5,6)7;;/h2*1,3-4H2,2H3;(H,5,6,7);;/q;;;+1;/p-1/f2C4H9.CF3O3S.Sn.H/q;;-1;m;/rC9H19F3O3SSn/c1-3-5-7-17(8-6-4-2)15-16(13,14)9(10,11)12/h17H,3-8H2,1-2H3

InChIKey = XEKRYMDPMIPXGW-RFGPJLDECH

(lewis acidic stannane, reagent for hydrostannation of alkenols and alkynols)

Physical Data: IR (neat) 2960, 2927, 2862, 1903 (Sn–H), 1323, 1209, 1016 cm^{-1}; ^1H NMR (C_6D_6) δ 0.93 (t, J = 7.3 Hz, 6H), 1.15–1.93 (m, 12H), 8.99 (br s, ^1J (^{119}Sn–^1H) = 2336 Hz, ^1J (^{117}Sn–^1H) = 2233 Hz, 1H); ^{13}C NMR (C_6D_6) δ 13.60 (CH_3 × 2), 21.02 (br, CH_2 × 2, 1J (Sn –^{13}C) = 435 Hz), 26.71 (CH_2 × 2, ^3J (^{119}Sn–^{13}C) = 83.3 Hz, ^3J (^{117}Sn–^{13}C) = 79.9 Hz), 27.88 (br, CH_2 × 2, ^2J (Sn–^{13}C) = 30 Hz), 119.30 (q, ^1J (^{19}F–^{13}C) = 317 Hz); ^{119}Sn NMR (C_6D_6) δ 22.7.

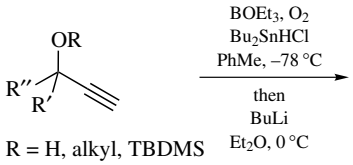
Preparative Methods: prepared by reaction of equimolar amounts of TfOH and Bu_2SnH_2.

Purification: used directly after preparation.

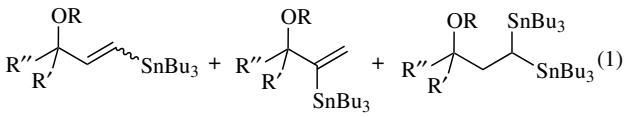
Handling, Storage, and Precautions: can be stored up to a week under N_2 at 4 °C. Long-term storage results in decomposition to distannanes. Attempts at distillation resulted in disproportionation to give Bu_2SnH_2.

General Reactivity. This reagent was recently introduced as an alternative to Bu_2SnHCl having enhanced Lewis acidic character for hydrostannation of unsaturated alcohols.

Hydrostannation of Alkynols. Dibutyl(trifluoromethanesulfoxy)stannane was first introduced as a reagent for hydrostannation of alkynols other than propargylic alcohols.[1] The authors had previously described the use of Bu_2SnHCl for the free radical hydrostannation of propargylic alcohols (eq 1).[2] A key controlling element in this methodology was coordination of the tin center to the oxygen atom,[1,2] which allows for suppression of isomerization of the *Z*- to *E*-vinylstannane (eq 2).[1]

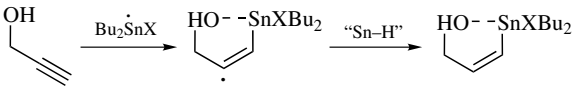


R = H, alkyl, TBDMS
R′, R″ = H, alkyl



R = alkyl, yield: 72–87% (*Z*:*E* > 89:11) 6–12% traces
R = H, yield: 71–96% (*Z*:*E* > 96:4)

(1)

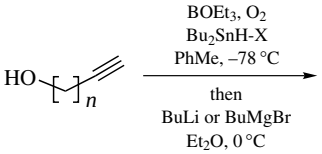


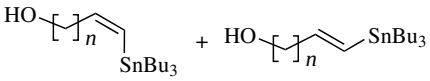
(2)

Drawbacks of this method are poor yields and stereoselectivity for substrates having longer spacers between the alcohol and alkyne functionalities (eq 3). As the unsubstituted chain was elongated from one to three methylene units, the yield of *Z*-vinyl stannane decreased dramatically while the yield of the *E*-isomer increased. However, when $Bu_2SnHOTf$ is employed, consistently high yields are obtained for all linker lengths.

When the alkyne moiety of a propargyl alcohol is internal rather than terminal, the nature of the flanking substituent can influence the regiochemistry of the hydrostannation when Bu_2SnHCl is

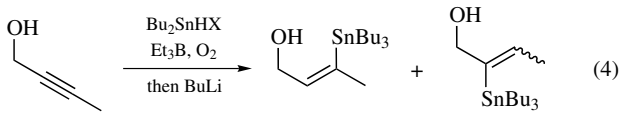
employed (eq 4). However, $Bu_2SnHOTf$ is superior to Bu_2SnHCl in this application in terms of yield and regioselectivity.





(3)

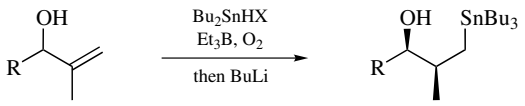
n	X	(%)	(%)	Reference
1	Cl	71	0	2
2	Cl	30	13	2
3	Cl	17	50	2
1	OTf	85	0	1
2	OTf	80	0	1
3	OTf	76	5	1
4	OTf	61	19	1



(4)

X	Yield (%)	Product ratio	Reference
Cl	70	2:98	1
OTf	88	71:26	1

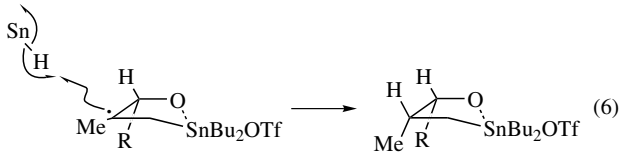
Hydrostannation of Alkenols. The free radical initiated hydrostannation reaction described above has been applied to allylic and homoallylic alcohols.[3] The reaction was first optimized for secondary allylic alcohols where the olefin is 1,1-disubstituted (eq 5), which provides the corresponding γ-stannylated secondary alcohols in excellent *syn*-diastereoselectivity and chemical yield. The reaction works best in apolar solvents such as hexane and delivers superior diastereoselectivity when $Bu_2SnHOTf$ is employed rather than Bu_2SnHCl. The size of the R group attached to the α-carbon influences the stereochemical outcome of the reaction, where larger groups lead to higher *syn*-selectivity, albeit at slightly lower yields.



(5)

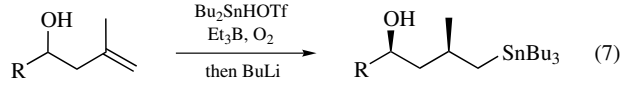
R	Solvent	X	Yield (%)	*syn*/*anti*
Ph	Et_2O	Cl	72	79:21
Ph		OTf	75	97:3
Me	Hexane	OTf	88	84:16
i-Pr		OTf	75	95:5
t-Bu		OTf	71	97:3

As was the case with the hydrostannation of alkynols, chelation between the Lewis acidic tin and oxygen atoms within a radical intermediate plays a key role in the outcome of the reaction. In the case of allylic alcohols, a five-membered radical intermediate abstracts hydrogen from $Bu_2SnHOTf$ in such a way to minimize steric interactions imposed by the chiral α-center (eq 6).



(6)

Homoallylic alcohols are also hydrostannylated with excellent regioselectivity and good diastereoselectivity (eq 7). Here, the authors note again that the diastereoselectivity was higher in hexane compared to Et_2O, but that the stereochemical outcome was less dependent on the steric size of the α-substituent.



(7)

R	Yield (%)	*syn*/*anti*
Ph	94	94:6
Me	96	90:10
i-Pr	92	90:10
t-Bu	96	93:7

1. Miura, K.; Wang, D.; Matsumoto, Y.; Hosomi, A., *Org. Lett.* **2005**, *7*, 503.
2. Miura, K.; Wang, D.; Matsumoto, Y.; Fujisawa, N.; Hosomi, A., *J. Org. Chem.* **2003**, *68*, 8730.
3. Miura, K.; Wang, D.; Hosomi, A., *J. Am. Chem. Soc.* **2005**, *127*, 9366.

Lee Fader
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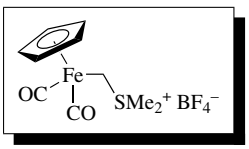
Dicarbonyl(cyclopentadienyl)[(dimethylsulfonium)methyl]iron Tetrafluoroborate[1]



[72120-26-4] $C_{10}H_{13}BF_4FeO_2S$ (MW 339.93)

InChI = 1/C5H5.C3H8S.2CO.BF4.Fe/c1-2-4-5-3-1;1-4(2)3;2*1-2;2-1(3,4)5;/h1-5H;1H2,2-3H3;;;;/q;+1;;;-1;
/rC5H5.C3H8FeS.2CO.BF4/c1-2-4-5-3-1;1-5(2)3-4;2*1-2;2-1(3,4)5/h1-5H;3H2,1-2H3;;;/q;+1;;;-1

InChIKey = IUCMQNISYUCLTH-LCVQXYBJAK

(stable precursor of a cationic carbene, or methylene, complex of iron; reacts directly with alkenes to give cyclopropanes[2])

Physical Data: mp 129–130 °C; *d* 1.57 g cm^{-3}.

Solubility: insol or slightly sol most solvents at rt; sol very polar solvents such as nitromethane at rt; sol other polar solvents (e.g. dioxane) at reflux.

Form Supplied in: yellow–orange powder or crystals.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: the preparation of this reagent has gone through several revisions and improvements since its introduction in 1979. The most recently improved preparations[3] are satisfactory for large-scale applications and have been adapted for commercial use. In a one-pot operation, the stable, crystalline, dinuclear complex $[Cp(CO)_2Fe]_2$ is reductively cleaved with sodium dispersion to generate a THF solution of the highly nucleophilic sodium ferrate, $Na[Cp(CO)_2Fe]$. This species is immediately alkylated with chloromethyl methyl sulfide, and the resulting iron alkyl, $Cp(CO)_2FeCH_2SMe$, is subjected to *S*-alkylation with methyl iodide. Finally, the resulting sulfonium salt, initially produced as an iodide, is subjected to in situ anion exchange and simultaneous crystallization by treatment with hot aqueous $NaBF_4$, followed by cooling to give the reagent as a yellow–orange, or amber-colored, crystalline solid (eq 1) which has been characterized spectroscopically and by single-crystal X-ray diffraction.[4] The anion exchange is performed in order to assure that a nonnucleophilic counterion is present during the subsequent cyclopropanation reactions; a nucleophilic anion such as iodide may apparently intercept reactive intermediates on the pathway leading to the desired cyclopropane products. A remarkable property of the reagent is its unusually high stability compared to most other organometallic reagents. This point is especially clear from the fact that it can be recrystallized from hot water exposed to the air.

Purification: recrystallization from nitromethane, acetone, or other polar solvents.

$$[Cp(CO)_2Fe]_2 \xrightarrow[\text{THF}\\ \text{reflux}]{\text{Na metal}} \{Na[Cp(CO)_2Fe]\} \xrightarrow[\text{THF}\\ \text{0–25 °C}]{ClCH_2SMe}$$

$$[Cp(CO)_2FeCH_2SMe] \xrightarrow[\text{THF}\\ \text{25 °C}]{MeI} [\,Cp(CO)_2FeCH_2SMe_2^+\,I^-] \xrightarrow[H_2O\\ \text{95 °C}]{NaBF_4}$$

$$Cp(CO)_2FeCH_2SMe_2^+\,BF_4^- \quad (1)$$

Handling, Storage, and Precautions: stable indefinitely as a solid, even when exposed to air; slowly decomposes in solution if exposed to air for long periods of time (although reactions with alkenes can be done in the presence of air and even moisture); decomposes upon heating to release dimethyl sulfide (stench). Use in a fume hood.

Alkene Cyclopropanation. Once this reagent has been prepared (or purchased commercially) it can be used directly in reactions with a wide range of alkenes without the need for using any further activation agents in order to obtain cyclopropanes (eq 2). An iron carbene complex is apparently generated as a reactive intermediate upon dissociation of dimethyl sulfide which ultimately recombines with the iron moiety to give the principal byproduct of the reaction.

$$Cp(CO)_2FeCH_2SMe_2^+\,BF_4^- + \xrightarrow[\text{polar solvent}]{\text{80–100 °C}}$$

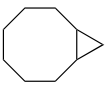
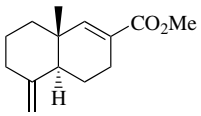
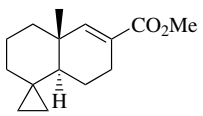
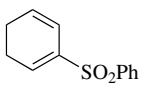
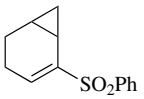
$$[Cp(CO)_2Fe{=}CH_2^+\,BF_4^-] \longrightarrow$$

$$+\ Cp(CO)_2Fe(SMe_2)^+\,BF_4^- \quad (2)$$

The procedure is very simple; the reagent and the alkene are mixed with a polar solvent and then heated in the temperature range of typically 80–100 °C for a few hours. Among the solvents that have been used successfully are 1,4-dioxane, DMF, ethanol, and nitromethane. The last of these, nitromethane, typically and reproducibly gives the highest yields of cyclopropanes. Excess reagent is commonly used to assure complete conversion of alkene to cyclopropane; 2 mol equiv is usually sufficient, but in some cases of less reactive alkene substrates the use of 3 mol equiv is necessary for obtaining optimum yields of cyclopropanes. The products are isolated very easily by adding pentane or another suitable nonpolar solvent to the cooled reaction mixture to precipitate the organometallic byproducts. Filtration of the mixture and use of routine distillation or chromatographic purification techniques then provide the cyclopropanes.

The reaction occurs most efficiently with mono- and disubstituted alkenes. More highly substituted alkenes generally react too slowly and exhibit very poor conversion to cyclopropanes. Some illustrative examples of efficient cyclopropanation are gathered in Table 1. Entries 1[2] and 2[2] are representative of relatively simple, nonfunctionalized alkenes. Entries 3[5] and 4[6] indicate both compatibility with other simple functional groups (ethers, sulfides, and acetals have also been used[2]) and the typical selectivity of an electrophilic reagent for more electron-rich alkenes in the presence of electron-deficient double bonds.

Table 1 Cyclopropanation of alkeneses with $Cp(CO)_2FeCH_2SMe_2^+$

Entry	Alkene	Product	Yield (%)
1			83
2			88
3			86
4			68

Alternative Reagents. The classical method for the addition of a simple methylene group to an alkene is the Simmons–Smith reaction.[7] Indeed, it is still probably the most highly used method for effecting this transformation. It is compatible with a wide range of functional groups, and it appears to be less sensitive to the degree of double bond substitution than the present iron reagent. On the other hand, the Simmons–Smith reagent appears to show reactivity towards both electron-deficient and electron-rich alkenes in some cases; the selectivity is less pronounced than in the case of the iron reagent. More specifically, the conversions shown in entries 3 and 4 of Table 1 were also attempted with the Simmons–Smith reagent, but the iron reagent gave superior results.[5,6] A minor disadvantage of the Simmons–Smith reaction is that the active reagent must be prepared freshly before use from diiodomethane and zinc/copper couple or related combinations of sometimes air-sensitive reagents,[8] whereas the iron reagent can be stored as a

highly stable solid for indefinite periods of time before use and then be used directly with no further activation being necessary. diazomethane may also be used as an alternative reagent,[1c] but the hazards and difficulties of preparing and handling this reagent are well known.

1. (a) Brookhart, M.; Studabaker, W. B., *Chem. Rev.* **1987**, *87*, 411. (b) Helquist, P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1991; Vol. 2, p 143. (c) Helquist, P., *Comprehensive Organic Synthesis* **1991**, *4*, 951.
2. (a) Brandt, S.; Helquist, P., *J. Am. Chem. Soc.* **1979**, *101*, 6473. (b) O'Connor, E. J.; Brandt, S.; Helquist, P., *J. Am. Chem. Soc.* **1987**, *109*, 3739.
3. (a) Mattson, M. N.; Bays, J. P.; Zakutansky, J.; Stolarski, V.; Helquist, P., *J. Org. Chem.* **1989**, *54*, 2467. (b) Mattson, M. N.; O'Connor, E. J.; Helquist, P., *Org. Synth.* **1992**, *70*, 177.
4. O'Connor, E. J. Helquist, P., *J. Am. Chem. Soc.* **1982**, *104*, 1869.
5. Wender, P. A.; Eck, S. L., *Tetrahedron Lett.* **1982**, *23*, 1871.
6. Bäckvall, J.-E.; Löfström, C.; Juntunen, S. K.; Mattson, M., *Tetrahedron Lett.* **1993**, *34*, 2007.
7. Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M., *Org. React.* **1973**, *20*, 1. See also ref. 1(c) for a more recent review.
8. Maruoka, K.; Fukutani, Y.; Yamamoto, H., *J. Org. Chem.* **1985**, *50*, 4412.

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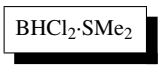
Dichloroborane–Dimethyl Sulfide[1]



[63462-42-0] $C_2H_7BCl_2S$ (MW 144.85)
InChI = 1/C2H6S.BCl2H/c1-3-2;2-1-3/h1-2H3;1H
InChIKey = MCBDXMRLVTYWJJ-UHFFFAOYAU

(hydroborating agent suitable for the hydroboration of labile alkenic structures;[2] provides access to alkyldichloroboranes and alkenyldichloroboranes[3,4])

Alternate Name: DCBS.
Physical Data: d_4^{20} = 1.255 g cm^{-3}.
Solubility: sol benzene, carbon tetrachloride, dichloromethane, diethyl ether, THF.
Form Supplied in: colorless to pale yellow liquid.
Analysis of Reagent Purity: hydrolyze an aliquot and measure the hydrogen evolved according to the standard procedure.[7a] ^{11}B NMR (CCl_4): δ, ppm, 2.0;[7b] 1.7 (d);[7c] 2.2 (d, J_{B-H} = 157.42 Hz).[5]
Preparative Methods: by redistribution of borane–dimethyl sulfide (BMS) and $BCl_3{\cdot}SMe_2$.[5] A mixture containing $BHCl_2{\cdot}SMe_2$ (73%) and BMS, $BH_2Cl{\cdot}SMe_2$, and $BCl_3{\cdot}SMe_2$ is obtained by the reaction of BMS with Ph_3CCl.[6]
Handling, Storage, and Precautions: corrosive, air- and moisture-sensitive, flammable liquid; stench. Reacts violently with water. Handle and store under nitrogen or argon. Stable indefinitely when stored under nitrogen at 25 °C. Destructive to upper respiratory tract, eyes, and skin. Handle in a fume hood.

Original Commentary

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Nicolaus Copernicus University, Torun, Poland

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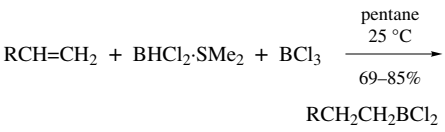
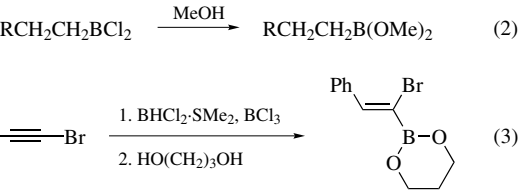
Hydroboration of Alkenes and Alkynes. The hydroboration of alkenes with dichloroborane–dimethyl sulfide (DCBS) in refluxing dichloromethane produces considerable quantities of R_2BCl and R_3B as impurities, presumably as the result of disproportionation of the reagent. The addition of boron trichloride liberates dichloroborane and the hydroboration proceeds cleanly at 25 °C (eq 1).[3]



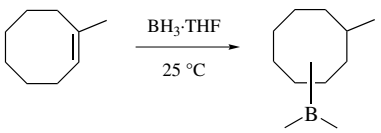
(1)

DCBS is highly regioselective,[8] exhibiting the directive effects similar to those observed for monochloroborane diethyl etherate.[9] Alkyldichloroboranes are readily isolated by distillation under vacuum. Methanolysis provides the corresponding alkylboronic esters (eq 2).[3] Alkenylboronic esters can be obtained from alkynes (eq 3).[4]

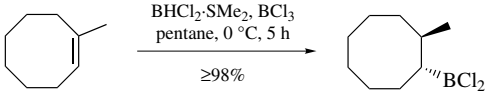


(2) (3)

A characteristic feature of alkyldichloroboranes is their exceptional resistance to thermal isomerization, making possible the regio- and stereoselective synthesis of organoborane intermediates from highly labile alkenic structures. Thus the organoborane intermediate initially formed in the hydroboration of 1-methylcyclooctene with borane–tetrahydrofuran undergoes facile isomerization, even at 0 °C, to a mixture of regio- and stereoisomeric organoboranes (eq 4).[10] In contrast, the hydroboration of 1-methylcyclooctene with DCBS at 0 °C affords cleanly *trans*-(2-methylcyclooctyl)dichloroborane in excellent yield and purity (eq 5).[2]



(4)

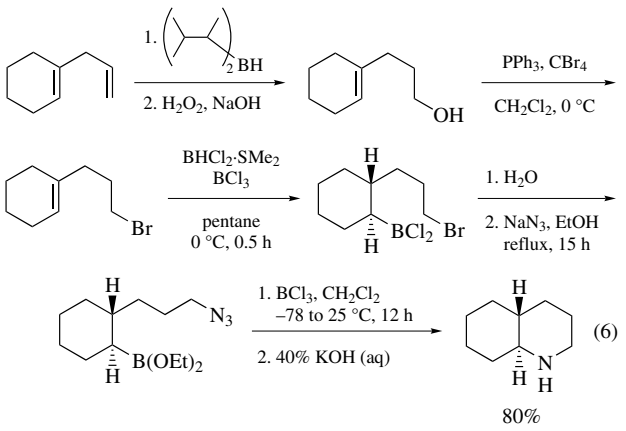


(5)

≥99% purity

An intramolecular version of the reaction of alkyldichloroboranes with organic azides has been employed in a highly

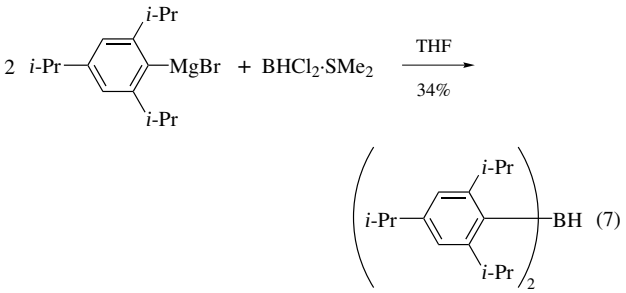
stereoselective synthesis of *trans*-cycloalkanopiperidines and cycloalkanopyrrolidines (eq 6)[11] (for the synthesis of other secondary amines).



(6)

Alkyldichloroboranes can be converted into a host of valuable organoborane intermediates via the hydridation–stepwise hydroboration procedure.[12] The procedure enables a general synthesis of unsymmetrical dialkylboranes and totally mixed trialkylborane intermediates for the synthesis of ketones and tertiary alcohols, respectively.[12b]

Transmetalation. The reagent has been used in the synthesis of bis(2,4,6-triisopropylphenyl)borane ((trip)$_2$BH) by the transmetalation reaction (eq 7).[13] (Trip)$_2$BH belongs to the family of highly hindered borane reagents like dimesitylborane.[14] It is a rare example of a monomeric disubstituted borane.[13]



(7)

First Update

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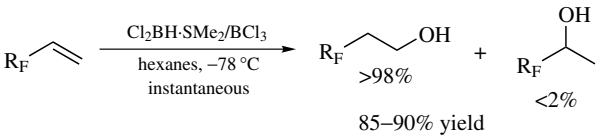
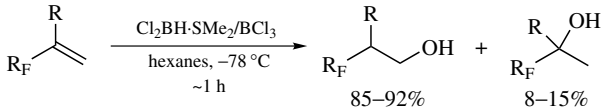
Purdue University, West Lafayette, IN, USA

Hydroboration of Fluoroolefins. Fluoroorganic compounds are valuable intermediates in analytical, biological, medicinal, organic, polymer, and materials chemistry. Hydroboration of perfluoroolefins with hydroborating agents provides easy access to fluoroalkylboranes, which can be readily converted to a variety of fluoroorganic compounds. For example, BH_3·Me_2S and BH_3·THF react with perfluorinated terminal alkenes to provide a mixture of 2 °/1 ° alcohols in a ratio 7:3 upon alkaline oxidation. Fluoroolefins also undergo facile hydroboration with Chx_2BH. However, they are too slow to react with 9-BBN. Catecholborane and pinacolborane react with fluoroolefins in the presence of a transition metal catalyst. However, reactive boranes, such as dichloroborane-methyl sulpfide readily react with mono, and disubstituted terminal perfluoroalkenes in the presence of BCl_3. The latter coordinates to Me_2S and releases the free dichloroborane, which instantaneously hydroborates the perfluoroalkenes. Oxidation under alkaline conditions furnishes the primary alcohol in >98% regioselectivity (eq 8).[15] Alternatively, the free dichloroborane prepared via Matteson's protocol[16] can also be used for the hydroboration of fluoroolefins.



R_F = CF_3, C_6F_5, C_6F_9, C_8H_{13}, etc.

(8)

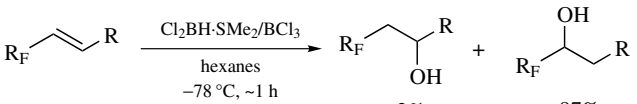


R_F = CF_3, C_6F_5, etc.

R = CH_3, C_8H_{17}, etc.

85–90% yield

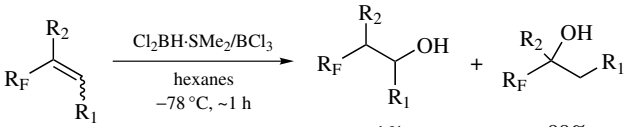
In contrast, 1,2-disubstituted and 1,1,2-trisubstituted fluorinated alkenes undergo hydroboration with $BHCl_2$ to yield the secondary and tertiary alcohols, respectively, in high regioselectivity and yields (eq 9).[17] During the hydroboration, the boron atom is placed on the carbon bearing the perfluoroalkyl substituent as long as the difference in the degree of substitution is ≤1 as in a 2 ° vs. 1 °, 2 ° vs. 2 °, or 3 ° vs. 2 ° carbon. When the selection is between a 3 ° and a 1 ° carbon, the steric effects surrounding the carbon dominate the electronic effects of the perfluoroalkyl substituent.



R_F = CF_3, C_6F_5, C_4F_9, etc.

R = CH_3, C_6H_5, C_5H_{11}, etc.

(9)

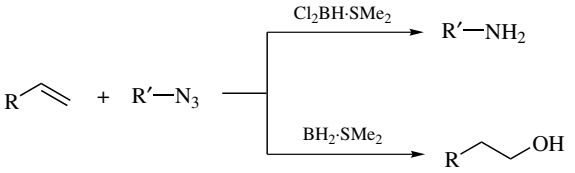


R_F = CF_3, C_6F_5, etc.

R_1, R_2 = CH_3, C_2H_5, etc.

Chemoselective Reduction of Azides. Organic azides undergo facile reduction with dichloroborane-methyl sulphide.[18] The rate of reduction is considerably faster than other borane reducing agents, such as BH_3·Me_2S or BH_3·THF. A judicious choice of the reagent leads to either the chemoselective reduction of azides in the presence of olefins or the hydroboration of olefins

in the presence of azides. Thus, the reaction of dichloroborane with a mixture of 1-decene and *n*-hexyl azide yields *n*-hexylamine chemoselectively. The same mixture undergoes hydroboration exclusively to yield 1-decanol upon treatment with $BH_3{\cdot}Me_2S$ (eq 10).[18]

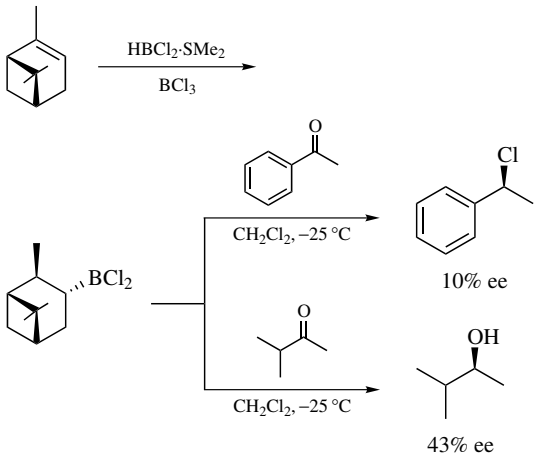


(10)

R′ = Alk, Ar, etc.

R = Alk, Ar, etc.

Reduction of Ketones Using Isopinocampheyldichloroborane, $IpcBCl_2$. B-Chlorodiisopinocampheylborane (Ipc_2BCl, DIP Chloride™) is an excellent reagent for the asymmetric reduction of a wide variety of prochiral ketones.[19] The proposed mechanism for the reduction with Ipc_2BCl suggests that one isopinocampheyl group on boron is sufficient for chiral induction.[19] However, studies involving the substitution of the second Ipc group with alkyl groups such as Me, Et, ^{i}Pr, ^{t}Bu, and thexyl revealed the importance of second Ipc group for the asymmetric induction. In a related study, $IpcBCl_2$ has also been utilized for the reduction of prochiral ketones furnishing the corresponding alcohol in 40–50% ee (eq 11).[20]

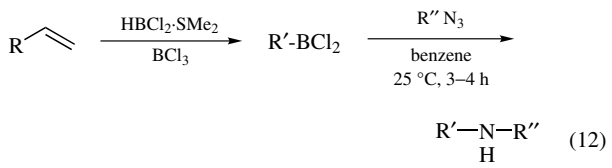


(11)

Under similar conditions, acetophenone did not furnish any reduction product upon workup with triethanolamine. Instead, α-phenethyl chloride was obtained in 10% ee.[20]

Preparation of 2°-Amines Using Alkyldichloroboranes, $RBCl_2$. Organyl azides undergo facile reaction with alkyldichloroboranes (readily prepared via the hydroboration of alkenes with dichloroborane) to provide the corresponding secondary amines (eq 12).[21]

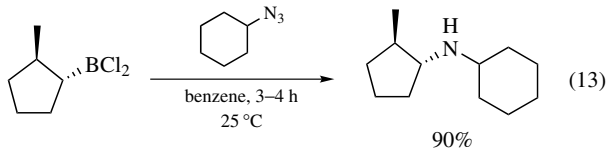
The reaction proceeds with absolute retention of stereochemistry at the carbon attached to boron. Thus, *trans*-2-methylcyclopentyl dichloroborane reduces cyclohexyl azide producing *trans*-2-methylcyclopentyl cyclohexylamine with complete retention of the *trans*-geometry (eq 13).[21]



(12)

R′ = *n*-Butyl, 2-Methyl-1-pentyl, 3-Hexyl, Cyclopentyl, Cyclohexyl, *exo*-Norbornyl etc.

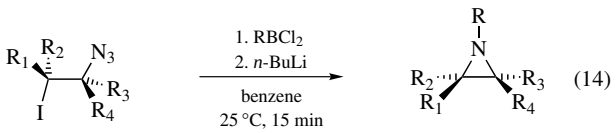
R″ = *n*-Butyl, Phenyl, Cycohexyl



(13)

90%

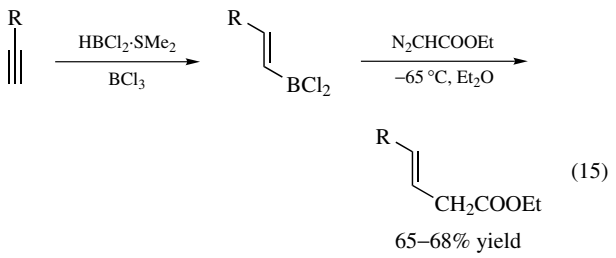
This reaction has been extended further for the preparation of *N*-substituted aziridines. β-Iodoazides undergo reduction with $RBCl_2$ producing the β-iodoamines that cyclize under basic conditions to furnish the *N*-substituted aziridines with complete stereochemical control around the aziridine ring (eq 14).[21]



(14)

80–92% yield

Preparation of β,γ-Unsaturated Carboxylic Esters. Brown and Salunkhe reported an analogous reaction involving (*E*)- or (*Z*)-1-alkenyldichloroboranes and ethyl diazoacetate for the synthesis of β,γ-unsaturated carboxylic esters (eq 15).[22]

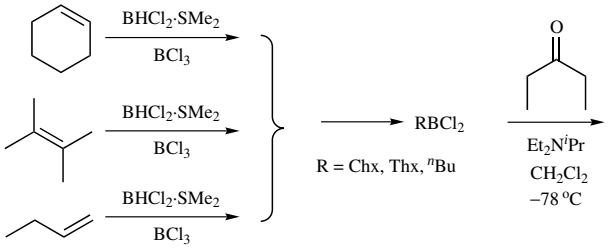


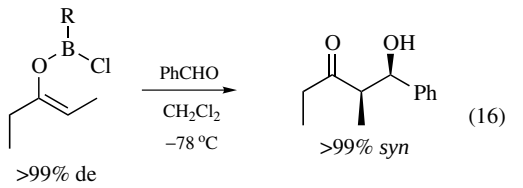
(15)

65–68% yield

R = *n*-Bu, *i*-Pr, Ph, cyclopentyl, etc.

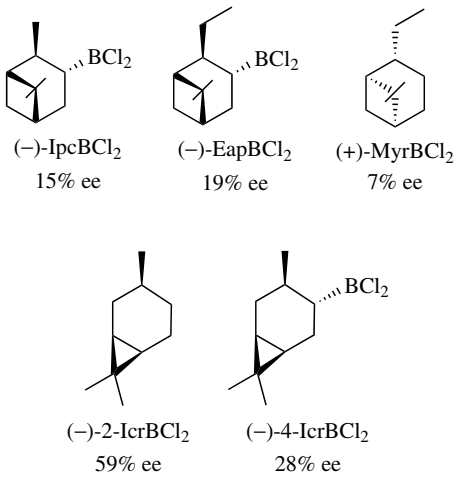
Enolboration Using Alkyldihaloboranes, $RBCl_2$. Dialkylhaloboranes such as Ipc_2BCl, Chx_2BCl, etc. have traditionally been used in the enolboration of carbonyl compounds.[23] More recently, alkyldihaloboranes prepared via the hydroboration of alkenes with dichloroborane-methylsulfide, have also been utilized for the *syn*-selective enolboration of ketones (eq 16).[24] Thus the reaction of 3-pentanonewith a series of alkyl dichloroboranes yielded the (Z)-enolborinates, which upon reaction with an aldehyde ketone provide the corresponding β-hydroxy ketones. The reaction was observed to be highly diastereoselective, favoring the *syn*-product (>99% de). It is interesting to note that, while R_2BCl gives the *E*-enolates and the *anti*-aldols, $RBCl_2$ furnishes the *Z*-enolates and *syn*-aldol product.





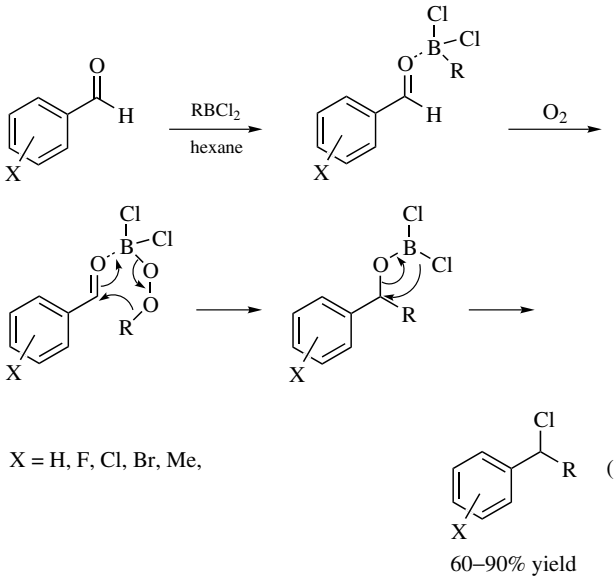
(16)

An enantioselective version of the above reaction was later developed by utilizing the chiral terpenyldichloroborane reagents.[25] These borane reagents were prepared via the hydroboration of the corresponding terpenes with dichloroborane. α-Pinene-derived chiral reagent $IpcBCl_2$ provided 15% ee of the *syn*-product. Increasing the steric bulk at the 2-position of the apopinene moiety resulted in a moderate increase of ee to 19%. β-Pinene-derived reagent provided very low ee, while significant increase in ee was observed with 2-isocaranyldichloroborane, $IcrBCl_2$ (59% ee).

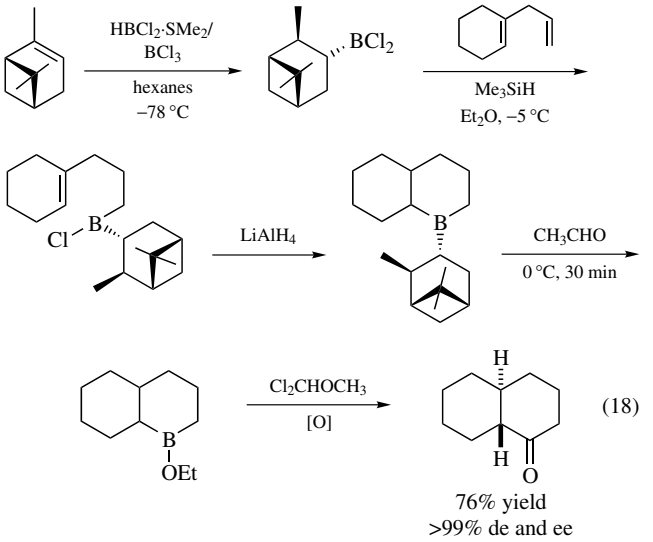


Alkylation of Aldehydes. Aldehydes react with alkyldihaloboranes in the presence of O_2 to produce the corresponding 2 °-alkyl halides in moderate to good yields. The initial coordination of $RBCl_2$ to the carbonyl is followed by the migration of alkyl group to the carbonyl carbon and the chlorination of the borinate intermediate to produce the halide products (eq 17).[26]

Carbonylation. Dialkylchloroboranes have also been used in the preparation of asymmetric ketones via reduction-hydroboration-carbonylaton protocol. In the presence of 1.0 equiv of trimethyl silane, $IpcBCl_2$ is reduced to IpcBHCl, which selectively hydroborates terminal olefins faster than internal olefins, furnishing the dialkyl chloroborane. Upon further reduction of the R_2BCl with $LiAlH_4$, the internal olefin undergoes hydroboration yielding the trialkylborane. Reaction of the resulting trialkylborane with an aldehyde results in the elimination of α-pinene furnishing the borinate, which upon carbonylation with dichloromethyl methyl ether, provides the corresponding cyclic ketones (eq 18).[27]



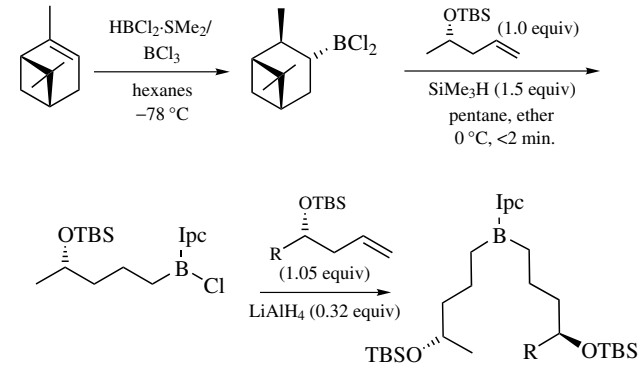
(17)

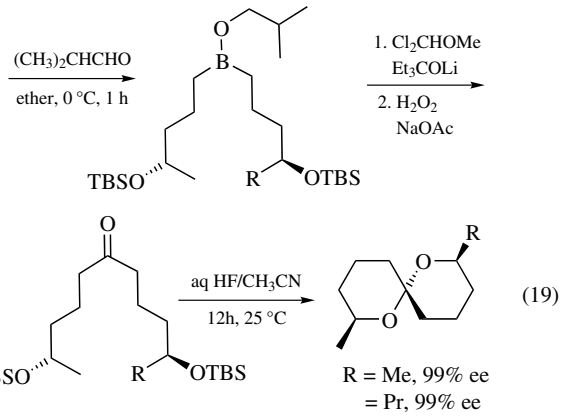


(18)

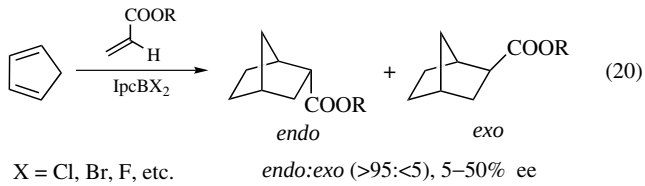
Brown et al. reported the stereoselective preparation of spiroketals via an extension of the above protocol involving the stepwise hydroboration of protected chiral homoallylic alcohols with $IpcBCl_2$ (eq 19).[28]

Applications in Diels–Alder Chemistry. Alkyldihaloboranes have also been used as chiral catalysts for the stereocontrolled Diels-Alder Chemistry.[29] High *endo*-selectivity is observed for this reaction although the ee's are only in the range of 5–50% (eq 20).





(19)



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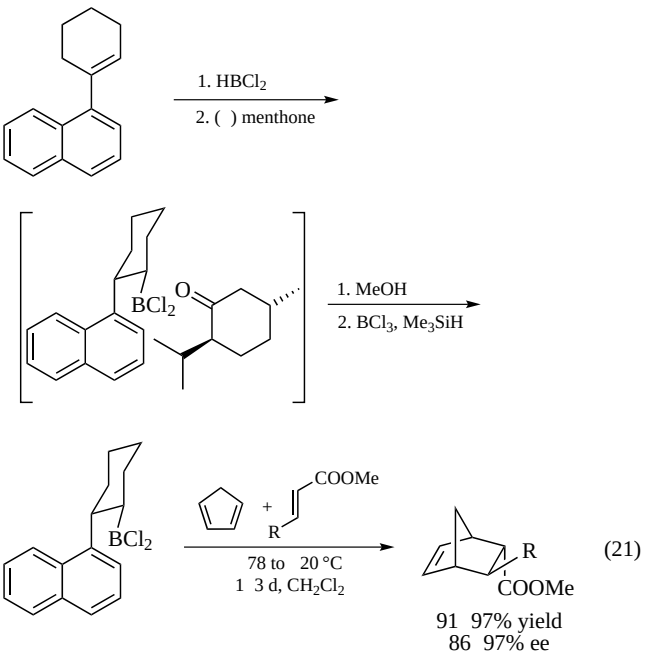


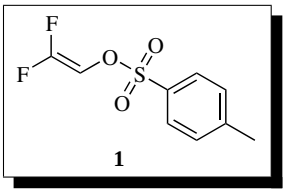
(21)

Hawkins et al. [30] observed that the reaction of α, β-unsaturated esters with cyclopentadiene in the presence of catalytic (1*R*, 2*R*)-2-naphthalenyl-cyclohexyldichloroborane leads to the enantioselective formation of Diels-Alder adducts in high yield and ee (87–97% ee). The borane reagent is prepared via hydroboration of 1-(1-cyclohexenyl)naphthalene with dichloroborane to yield the racemic product, which was later resolved via its crystalline complex with (−)-menthone to furnish >99% de after one recrystallization. The menthone-free catalyst was obtained by methanolysis, followed by rechlorination with BCl_3 (eq 21).

1. (a) Brown, H. C.; Zaidlewicz, M., *Polish J. Appl. Chem.* **1982**, *26*, 155. (b) Brown, H. C.; Kulkarni, S. U., *J. Organomet. Chem.* **1982**, *239*, 23. (c) Pelter, A.; Smith, K., *Comprehensive Organic Synthesis* **1991**, *8*, 703.
2. Brown, H. C.; Racherla, U. S., *J. Org. Chem.* **1983**, *48*, 1389.
3. Brown, H. C.; Ravindran, N.; Kulkarni, S. U., *J. Org. Chem.* **1980**, *45*, 384.
4. Brown, H. C.; Bhat, N. G., *J. Org. Chem.* **1988**, *53*, 6009.
5. Brown, H. C.; Ravindran, N., *Inorg. Chem.* **1977**, *16*, 2938.
6. Bolton, R.; Gates, P. N.; Jones, S. A. W., *Aust. J. Chem.* **1987**, *40*, 987.
7. (a) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975; p 239. (b) Paget, W. E.; Smith, K., *J. Chem. Soc., Chem. Commun.* **1980**, 1169. (c) Shiner, C. S.; Garner, C. M.; Haltiwanger, R. C., *J. Am. Chem. Soc.* **1985**, *107*, 7167.
8. Brown, H. C.; Racherla, U. S., *J. Org. Chem.* **1986**, *51*, 895.
9. Brown, H. C.; Ravindran, N., *J. Am. Chem. Soc.* **1976**, *98*, 1785.
10. (a) Brown, H. C.; Zweifel, G., *J. Am. Chem. Soc.* **1961**, *83*, 2544. (b) Brown, H. C.; Klimisch, R. L., *J. Am. Chem. Soc.* **1966**, *88*, 1430.
11. Brown, H. C.; Salunkhe, A. M., *Tetrahedron Lett.* **1993**, *34*, 1265.
12. (a) Brown, H. C.; Kulkarni, S. U., *J. Organomet. Chem.* **1981**, *218*, 299. (b) Kulkarni, S. U.; Basavaiah, D.; Zaidlewicz, M.; Brown, H. C., *Organometallics* **1982**, *1*, 212.
13. Bartlett, R. A.; Diaz, H. V. R.; Olmstead, M. M.; Power, P. P.; Weese, K. J.; Tirpz, H. B., *Organometallics* **1990**, *9*, 146.
14. Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*, Academic: London, 1988; p 189 and 336.
15. Brown, H. C.; Chen, G. C.; Jennings, M. P.; Ramahcandran, P. V., *Angew. Chem. Int. Ed.* **1999**, *38*, 2052.
16. Matteson, D. S.; Soundararajan, R., *J. Org. Chem.* **1990**, *55*, 2274.
17. Ramachandran, P. V.; Jennings, M. P., *Org. Lett.* **2001**, *3*, 3789.
18. Salunkhe, A. M.; Ramachandran, P. V.; Brown, H. C., *Tetrahedron* **2000**, *58*, 10059.
19. (a) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C., *J. Org. Chem.* **1985**, *50*, 5446. (b) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V., *J. Org. Chem.* **1986**, *51* 3394. (c) Brown, H. C.; Chandrasekharan, J.; Ramahcandran, P. V., *J. Am. Chem. Soc.* **1988**, *110* 1539.
20. Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J., *Heteroatom. Chem.* **1995**, *6*, 117.
21. Brown, H. C.; Midland, M. M.; Levy, A. B.; Suzuki, A.; Sono, S.; Itoh, M., *Tetrahedron* **1987**, *43*, 4079.
22. Brown, H. C.; Salunkhe, A. M., *Synlett* **1991**, 684.
23. (a) Fenzl, W; Koster, R., *Leibegs. Ann. Chem.* **1975**, 1322. (b) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W., *Tetrahedron Lett.* **1989**, 1665. (c) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B., *J. Am. Chem. Soc.* **1989**, *111*, 3441. (d) Brown, H. C.; Ganesan, K.; Dhar, R. K., *J. Org. Chem.* **1992**, *57*, 3767. (e) Brown, H. C.; Ganesan, K.; Dhar, R. K., *J. Org. Chem.* **1993**, *58*, 147. (f) Ganesan, K.; Brown, H. C., *J. Org. Chem.* **1993**, *58*, 7162.
24. Ramachandran, P. V.; Xu, W-C.; Brown, H. C., *Tetrahedron Lett.* **1997**, *38*, 769.

25. Ramachandran, P. V.; Xu, W-C.; Brown, H. C., *Tetrahedron: Asymmetry* **1997**, *8*, 1379.
26. Kabalka, G. W.; Wu, Z.; Ju, Y., *Tetrahedron* **2002**, *58*, 3243.
27. Dhokte, U. P.; Pathare, P. M.; Mahindroo, V. K.; Brown, H. C., *J. Org. Chem.* **1998**, *63*, 8276.
28. Brown, H. C.; Kulkarni, S. V.; Racherla, U. S.; Dhokte, U. P., *J. Org. Chem.* **1998**, *63*, 7030.
29. (a) Bir, G.; Kaufmann, D., *Tetrahedron Lett.* **1987**, *28*, 777. (b) Bir, G.; Kaufmann, D., *J. Organomet. Chem.* **1990**, *390*, 1. (c) Kaufmann, D.; Boese, R., *Angew. Chem. Intl. Ed.* **1990**, *29*, 545.
30. Hawkins, J. M.; Loren, S., *J. Am. Chem. Soc.* **1991**, *113*, 7794.

2-2-Difluorovinyl *p*-Toluenesulfonate



1

[185739-14-4] $C_9H_8F_2O_3S$ (MW 234.2)

InChI = 1/C9H8F2O3S/c1-7-2-4-8(5-3-7)15(12,13)14-6-9(10)11/h2-6H,1H3

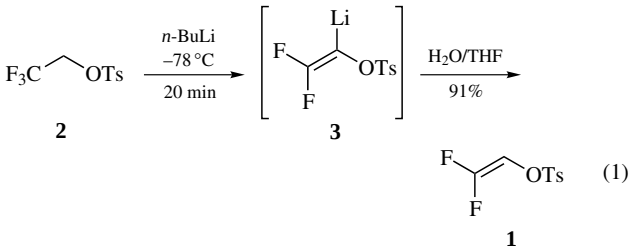
InChIKey = ZQLLPWMNXQYESO-UHFFFAOYAN

(an electrophilic fluorovinyl reagent that may be incorporated into various substrates either by cycloaddition[1] or by nucleophilic addition reactions[1])

Physical Data: colorless liquid.

Analysis of Reagent Purity: ^{1}H NMR, ^{13}C NMR, ^{19}F NMR.[2]

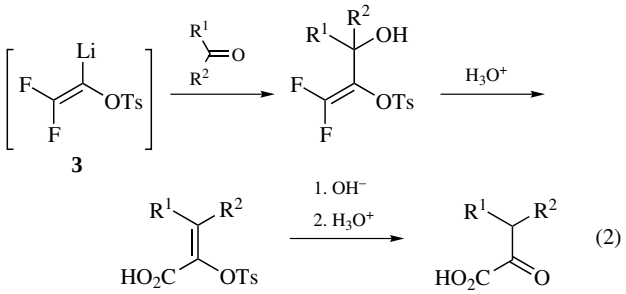
Preparative Methods: the reagent is prepared by the dropwise addition of 2 equiv of *n*-BuLi to commercially available 2,2,2-trifluoroethyl-*p*-toluenesulfonate (**2**) in THF followed by quenching of the resultant anion **3** with H_2O/THF (eq 1).[2] The intermediate fluorovinyl lithium anion **3** has also been prepared from **2** by reaction with LDA.[3–5]



2 **3** **1** (1)

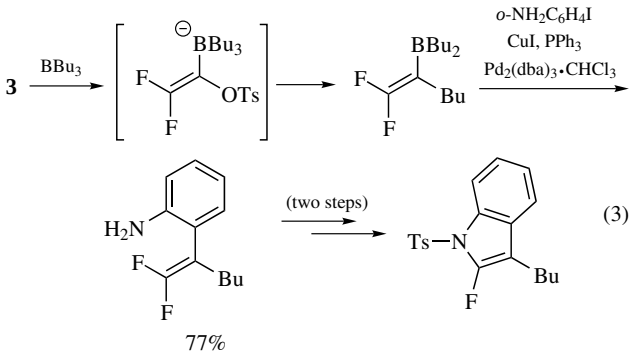
Purification: purified by silica gel chromatography (hexane: EtOAc 10:1).[2]

Anion Chemistry. The fluorovinyl anion **3** (eq 1) is a versatile intermediate and can be reacted with a variety of electrophiles. When treated with ketones, the anion gives secondary alcohols which can be sequentially hydrolyzed, firstly to carboxy enol-tosylates under acidic conditions, and then under basic conditions to give synthetically useful α-keto carboxylic acids (eq 2).[3]



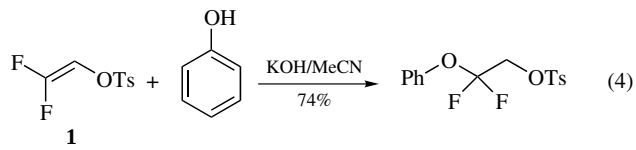
(2)

Reaction of the anion **3** with trialkyl boron compounds gives adducts which eliminate the toluenesulfonate group in a 1,2-alkyl shift (eq 3). The resultant vinyl boron compounds are capable of undergoing Suzuki-type cross-coupling reactions. Using this method, Ichikawa et al. were able to convert **3** into functionalized aryl adducts which were then cyclized in a 5-*endo trig* fashion to give monofluorinated adducts.[6]



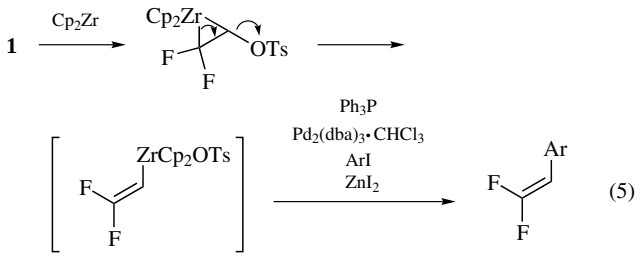
(3)

Nucleophilic Addition. The addition of both aliphatic and aromatic alcohols and thiols to **1** occurs under mild conditions to give stable saturated adducts in yields ranging from 53 to 74% (eq 4).[1] The nucleophilic addition is completely regioselective for the fluorinated carbon. It was shown that 1 equiv of KOH was required in order to achieve a high yield.



(4)

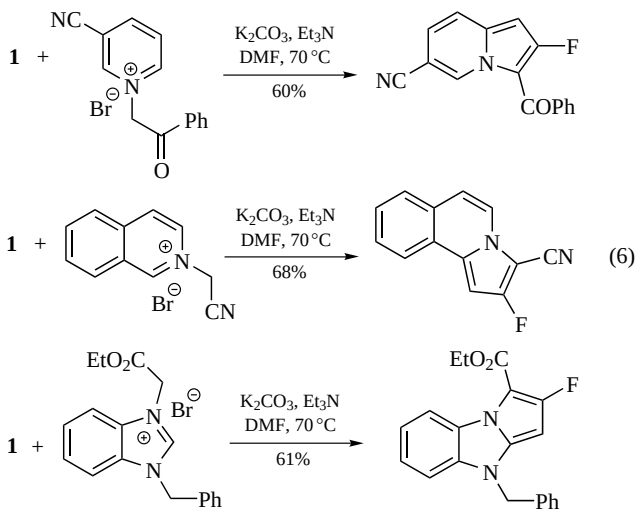
Zirconation. The reaction Cp_2Zr (generated in situ from Cp_2ZrCl_2 and 2 equiv of *n*-BuLi) with **1** generates a thermally stable 2,2-difluorovinyl zirconocene compound (eq 5). The reaction is thought to proceed through an intermediate zirconacyclopropane which undergoes β-elimination of *p*-toluenesulfonate giving the adduct. It was further shown that the zirconocene intermediate could undergo in situ transmetallation with zinc iodide followed by Negishi-type[7] cross-coupling with a variety of aryl iodides giving cross-coupled products in good to moderate yields.[6,8]



(5)

ArI (1.1 eq)	Yield (%)
p-$NO_2C_6H_4I$	76
p-$EtO_2CC_6H_4I$	78
PhI	71
1-NaphthylI	69
p-$MeOC_6H_4I$	62

Cycloaddition Reactions. The reaction of pyridinium, isoquinolinium, and benzimidazolinium *N*-ylide with fluorovinyl tosylate **1** gives cyclic monofluorinated adducts in moderate yield (eq 6). The reaction mechanism is thought to involve initial 1,3-dipolar cycloadditon of the *N*-ylide to **1**, followed by elimination of both tosic and hydrofluoric acid.[1]



(6)

1. Fang, X.; Wu, Y. M.; Deng, J.; Wang, S. W., *Tetrahedron* **2004**, *60*, 5487.
2. Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K., *Synthesis* **2002**, 1917.
3. Ichikawa, J.; Sonoda, T.; Kobayashi, H., *Tetrahedron Lett.* **1989**, *30*, 5437.
4. Tanaka, K.; Nakai, T.; Ishikawa, N., *Tetrahedron Lett.* **1978**, 4809.
5. Ichikawa, J.; Sonoda, T.; Kobayashi, H., *Tetrahedron Lett.* **1989**, *30*, 1641.
6. Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K., *Synthesis* **2002**, *13*, 1917.
7. Knochel, P.; Jones, P., *Organozinc Reagents*; Oxford University Press: New York, 1999.
8. Ichikawa, J.; Fujiwara, M.; Nawata, H.; Okauchi, T.; Minami, T., *Tetrahedron Lett.* **1996**, *37*, 8799.

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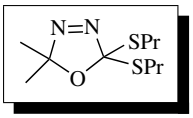
2,5-Dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole



[222625-77-6] $C_{10}H_{20}N_2OS_2$ (MW 248.41)
InChI = 1/C10H20N2OS2/c1-5-7-14-10(15-8-6-2)12-11-9(3,4)13-10/h5-8H2,1-4H3
InChIKey = FJYVPCVLZLZWFK-UHFFFAOYAF

(reagent used as bis(propylthio)carbene precursor)

Physical Data: solid at −78 °C, thermolysis occurs at 0 °C and above.

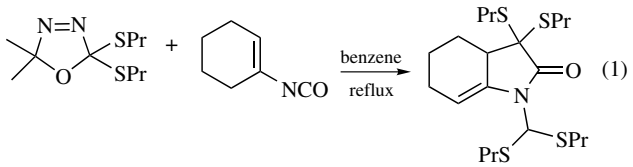
Solubility: hexanes, cyclohexane, dichloromethane, benzene, toluene, xylene.

Form Supplied in: colorless oil as synthesized.

Purity: column chromatography at 0 °C using hexanes–ethyl acetate (20:1); product elutes first; collect fractions in an ice bath; remove solvent in vacuo at 0 °C; dry under high vacuum at 0 °C for 1 h.

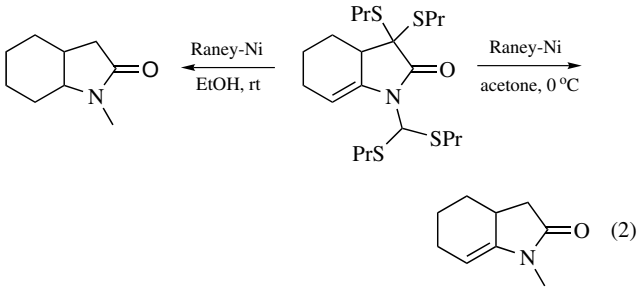
Handling, Storage, and Precautions: to prevent premature thermolysis, reagent should be stored in a sealed flask in a cooler with dry ice at −78 °C. Since the reagent is thermally labile and thermolysis is exothermic, avoid exposure to heat to prevent rapid evolution of nitrogen gas leading to a possible explosion. Thermolysis will occur at 0 °C and above. Use of an explosion shield and slow addition to refluxing solvents are recommended.

[1 + 4] Cycloaddition with Vinyl Isocyanates. Upon thermolysis in refluxing benzene, 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole yields the bis(propylthio)carbene precursor, which reacts as a 1,1-dipole equivalent in [1 + 4] cycloaddition reactions with various vinyl isocyanate substrates leading to highly functionalized adducts such as hydroindolones (eq 1).[1–3] Reductive desulfurization with Raney nickel yields the enamide or the fully reduced system (eq 2).[1] Cyclohexyl isocyanide also behaves as a 1,1-dipole equivalent in [1 + 4] cycloadditions with vinyl isocyanates, however the adducts are less functionalized.[4,5]



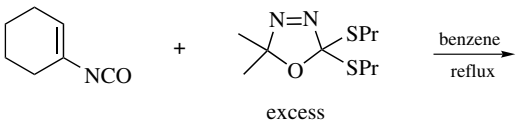
(1)

Dimethoxy carbene has been shown to behave as a carbonyl 1,1-dipole equivalent in [1 + 4] cycloadditions with vinyl isocyanates also yielding functionalized adducts.[6] However, the oxadiazole precursor requires higher thermolysis temperatures and hydrolysis of the acetals in the resultant adducts can be difficult for acid-sensitive systems.

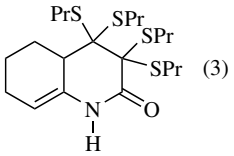


(2)

[4 + 1 + 1] Cycloaddition with Vinyl Isocyanate. When a large excess of 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole carbene precursor is added rapidly in refluxing benzene to a vinyl isocyanate, two equivalents of carbene add to the substrate prior to ring closure, leading to a six-membered adduct (eq 3).[1,2] However, no carbene insertion into the amide N–H bond occurs. This phenomenon is not observed with the dimethoxy carbene.[2]

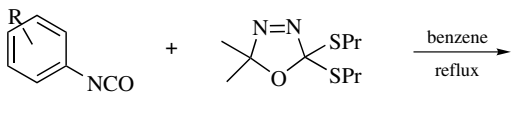


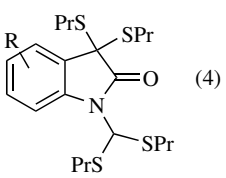
excess



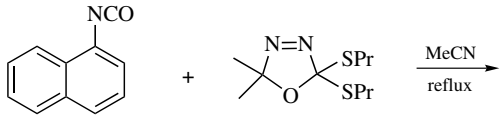
(3)

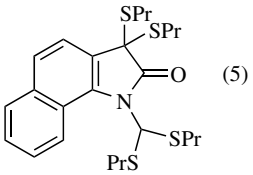
Addition of Bis(propylthio)carbenes to Aryl Isocyanates. Addition of 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole in refluxing benzene and an aryl isocyanate releases the bis(propylthio)carbene in situ which then adds easily to the aryl isocyanate to yield a substituted isatin with the ketone functionality protected as a thioacetal (eq 4).[7] Ring closure also occurred when the 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole carbene precursor was added to 1-naphthyl isocyanate in refluxing acetonitrile (eq 5).[7] Formation of thioacetal protected isatin products are unique to the bis(propylthio)carbene as other nucleophilic carbenes added to aryl isocyanates afforded only modest yields of hydantoin products.[8]





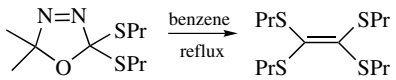
(4)





(5)

Dimerization. Upon thermolysis of 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole in refluxing benzene and in the absence of any electrophile, the resultant bis(propylthio)carbene will dimerize (eq 6).[1] Since the reaction is highly exothermic, care must be taken in the execution of this reaction. Use of an explosion shield and slow addition of the carbene precursor are recommended.



(6)

Related Reagents. Dimethoxy Carbene, Cyclohexyl Isocyanide.

1. Rigby, J. H.; Laurent, S., *J. Org. Chem.* **1999**, *64*, 1766.
2. Rigby, J. H.; Laurent, S.; Dong, W.; Danca, M. D., *Tetrahedron* **2000**, *56*, 10101.
3. Rigby, J. H.; Dong, W., *Org. Lett.* **2000**, *2*, 1673.
4. Rigby, J. H.; Deur, C.; Heeg, M. J., *Tetrahedron Lett.* **1999**, *40*, 6887.
5. (a) Rigby, J. H.; Qabar, M., *J. Am. Chem. Soc.* **1991**, *113*, 8975. (b) Rigby, JH.; Qabar, M.; Ahmed, G.; Hughes, R. C., *Tetrahedron* **1993**, *49*, 10219.
6. Rigby, J. H.; Cavezza, A.; Heeg, M. J., *J. Am. Chem. Soc.* **1998**, *120*, 3664.
7. Rigby, J. H.; Danca, M. D., *Tetrahedron Lett.* **1999**, *40*, 6891.
8. (a) Hoffmann, R. W.; Steinbach, K.; Dittrich, B., *Chem. Ber.* **1973**, *106*, 2174. (b) Lemal, D. M.; Gosselink, E. P.; McGregor, S. D., *J. Am. Chem. Soc.* **1966**, *88*, 582. (c) El-Saidi, M.; Kassam, K.; Pole, DL.; Tadey, T.; Warkentin, J., *J. Am. Chem. Soc.* **1992**, *114*, 8751. (d) Hoffmann, RW.; Reiffen, M., *Chem. Ber.* **1976**, *109*, 2565.

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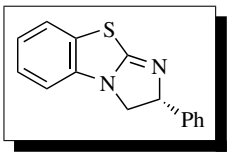
2,3-Dihydro-2-phenylimidazo[2,1-*b*]-benzothiazole



[885051-07-0] $C_{15}H_{12}N_2S$ (MW 252.33)

InChI = 1/C15H12N2S/c1-2-6-11(7-3-1)12-10-17-13-8-4-5-9-14(13)18-15(17)16-12/h1-9,12H,10H2/t12-/m0/s1

InChIKey = YGCWPCVAVSIFLO-LBPRGKRZBR

(2*S*-enantiomer)
[950194-37-3]
InChI = 1/C15H12N2S/c1-2-6-11(7-3-1)12-10-17-13-8-4-5-9-14(13)18-15(17)16-12/h1-9,12H,10H2/t12-/m1/s1
InChIKey = YGCWPCVAVSIFLO-GFCCVEGCBB

(enantioselective acylation catalyst useful for kinetic resolution (KR)[1] of benzylic[2] and propargylic alcohols[3] and oxazolidinones;[4]also utilized in desymmetrization of *meso*-diol lobelanidine[5])

Alternate Name: Benzotetramisole (BTM).

Physical Data: white solid; mp 94.5–95.0 °C (from Et_2O-hexanes); $[\alpha]_D = +256.7°$ (*c* 1.00, MeOH).

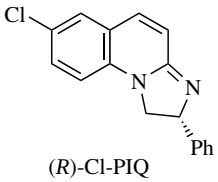
Solubility: soluble in common solvents, including $CHCl_3$, CH_2Cl_2, Et_2O, THF, MeCN, PhMe, DMF, *tert*-amyl alcohol, and MeOH. Slightly soluble in hexanes. Insoluble in H_2O.

Preparative Methods: prepared by heating 2-chlorobenzothiazole with (*R*)-(+)-phenylglycinol in the presence of diisopropylethylamine at 130 °C, followed by treatment of the resulting intermediate with methanesulfonyl chloride and triethylamine at 0 °C in CH_2Cl_2 and subsequent reflux.[2]

Purification: flash chromatography (5% *i*-PrOH, 1% NEt_3/hexanes) and recrystallization (Et_2O/hexanes).

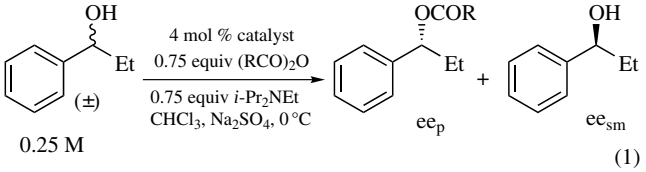
Handling, Storage, and Precautions: may be stored at room temperature. Should be protected from excessive humidity. Toxicity data are unavailable. The racemic compound has been shown to possess pharmacological activity.[6]

KR of Alcohols. KR of alcohols has traditionally relied on enzyme-catalyzed enantioselective transesterification and hydrolysis.[7–9] BTM and the closely related (2*R*)-7-chloro-1,2-dihydro-2-phenyl-imidazo[1,2-*a*]quinoline (Cl-PIQ)[10] are among the most easily obtainable and effective nonenzymatic enantioselective acylation catalysts[11] reported to date and thus represent a useful alternative to enzymes.



(*R*)-Cl-PIQ

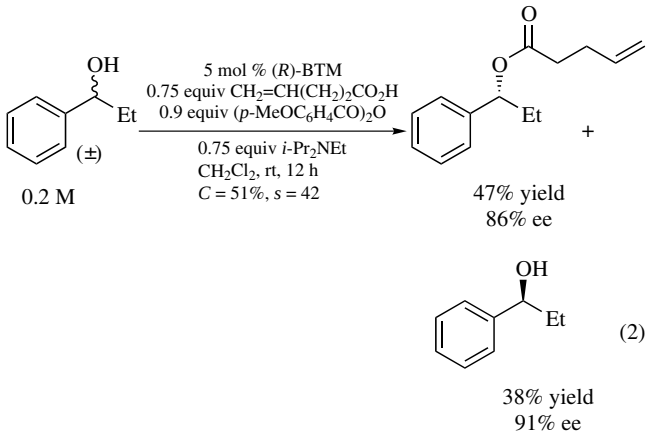
Both catalysts are especially suitable for the KR of benzylic alcohols (eq 1). Cl-PIQ is generally more catalytically active and achieves good to excellent enantioselectivity (selectivity factors *s* in the 30–100 range), while BTM is much more enantioselective (*s* in the 100–350 range).[12] Both propionic and isobutyric anhydrides have proved to be useful as achiral acyl donors in BTM-catalyzed acylations, the latter usually leading to higher enantioselectivities, but somewhat lower reaction rates. Cl-PIQ has been used primarily in combination with propionic anhydride. Chloroform is the solvent of choice in most cases. BTM-catalyzed reactions are sensitive to moisture (rapid catalyst deactivation) and, therefore, should be carried out in the presence of anhydrous Na_2SO_4.



(1)

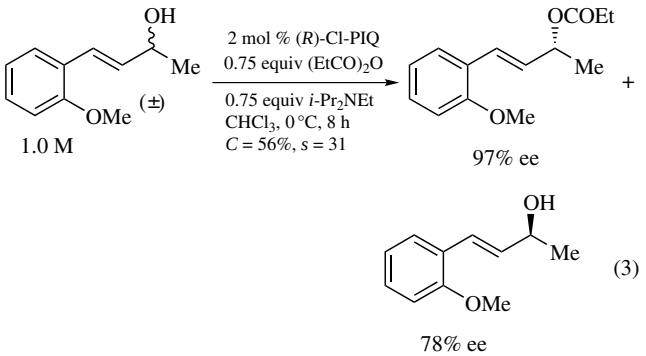
Catalyst	Anhydride	Time (h)	ee_p (%)	ee_{sm} (%)	*C* (%)	*S*
(*R*)-CI-PIQ	$(EtCO)_2O$	3.5	88	90	51	46
(*R*)-BTM	$(EtCO)_2O$	33	95	85	47	104
(*R*)-BTM	$(i\text{-PrCO})_2O$	36	97	82	46	144

A combination of free aliphatic carboxylic acids and benzoic anhydride derivatives may be employed to generate a variety of enantioenriched esters of benzylic alcohols via BTM-catalyzed KR (eq 2).[13]



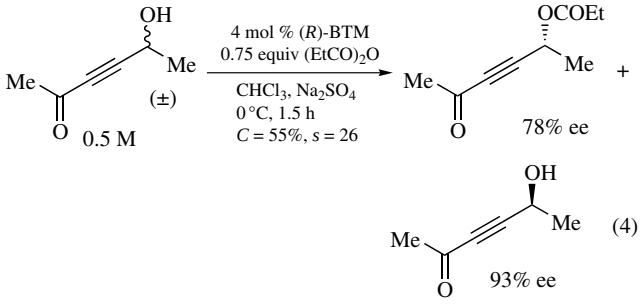
(2)

Cl-PIQ affords useful levels of enantioselectivity in KR of allylic alcohols (*s* in the 17–56 range) (eq 3).[10] BTM is generally less effective in this process.[2]



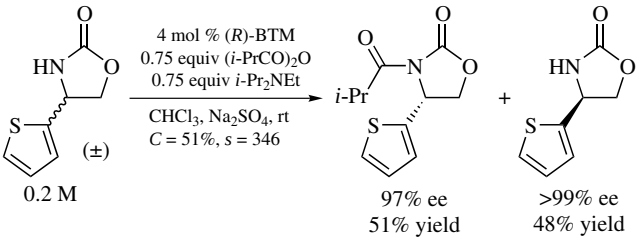
(3)

Propargylic alcohols can be resolved using BTM with selectivity factors up to 32, which is the highest ever achieved with nonenzymatic catalysts for this class of substrates (eq 4). Cl-PIQ affords lower enantioselectivities and reaction rates in this process.[3]



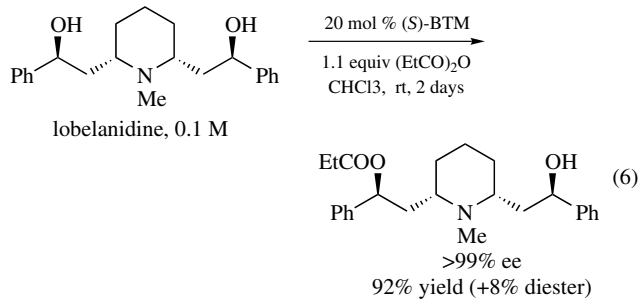
(4)

KR of Oxazolidinones. Unlike alcohols and amines, racemic oxazolidinones and other secondary lactams have never been resolved via enzymatic acylation. BTM has proved to be especially effective in KR of 4-aryl-substituted 2-oxazolidinones, affording selectivity factors in the 50–500 range in chloroform at room temperature (eq 5). Cl-PIQ is also suitable, but gives lower enantioselectivities (*s* in the 16–110 range in *tert*-amyl alcohol at 0 °C).[4]



(5)

Desymmetrization of *meso*-Diols. BTM-catalyzed desymmetrization of *meso*-diol lobelanidine has been employed as the key step in an asymmetric synthesis of alkaloid lobeline (eq 6).[5]



(6)

Related Reagents. 7-Chloro-1,2-dihydro-2-phenyl-imidazo [1,2-*a*]quinoline (Cl-PIQ), *R*-Enantiomer: [863319-04-4]);[10] 3,4-Dihydro-2-phenyl-2*H*-pyrimido[2,1-*b*]benzothiazole (HBTM);[14] 2-(*N*-Benzyl-*N*-methylaminomethyl)-1-methylpyrrolidine (*R*-Enantiomer: [540474-12-2], *S*-Enantiomer: [208833-00-5]);[15] 4-Dimethylaminopyridinyl(pentaphenylcyclopentadienyl)iron (C_5 Ph_5-DMAP, *R*-Enantiomer: [187682-64-0], *S*-Enantiomer: [187596-69-6]).[16]

1. Kagan, H. B.; Fiaud, J. C., *Top. Stereochem.* **1988**, *18*, 249.
2. Birman, V. B.; Li, X., *Org. Lett.* **2006**, *8*, 1351.
3. Birman, V. B.; Guo, L., *Org. Lett.* **2006**, *8*, 4859.
4. Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W., *J. Am. Chem. Soc.* **2006**, *128*, 6536.
5. Birman, V. B.; Jiang, H.; Li, X., *Org. Lett.* **2007**, *9*, 3237.
6. Amarouch, H.; Loiseau, P. R.; Bonnafous, M.; Caujolle, R.; Payard, M.; Loiseau, P. M.; Bories, C.; Gayral, P., *Farmaco Ed. Sci.* **1988**, *43*, 421.
7. Sih, C. J.; Wu, S.-H., *Top. Stereochem.* **1989**, *19*, 63.
8. Klibanov, A. M., *Acc. Chem. Res.* **1990**, *23*, 114.
9. Schoffers, E.; Golebiowski, A.; Johnson, C. R., *Tetrahedron* **1996**, *52*, 3769.
10. Birman, V. B.; Jiang, H., *Org. Lett.* **2005**, *7*, 3445.
11. Vedejs, E.; Jure, M., *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.
12. Selectivity factor is defined as s = *k*(fast-reacting enantiomer)/*k*(slow-reacting enantiomer). Both conversion *C* and selectivity factor *s* are calculated from ee's of the product (ee_p) and the recovered starting material (ee_{sm}) according to Kagan's equations: $C = ee_{sm}/(ee_p + ee_{sm})$; $s = \ln[(1-C)(1-ee_A)]/\ln[(1-C)(1+ee_A)]$.
13. Shiina, I.; Nakata, K., *Tetrahedron Lett.* **2007**, *48*, 8314.
14. Birman, V. B.; Li, X., *Org. Lett.* **2008**, *10*, 1115.
15. Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T., *Chem. Lett.* **1999**, 265.
16. Fu, G. C., *Acc. Chem. Res.* **2004**, *37*, 542.

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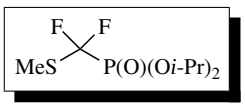
Diisopropyl Methylsulfanyldifluoromethylphosphonate

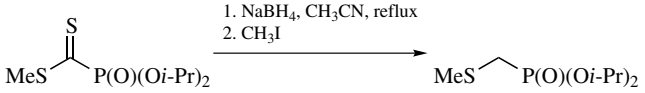


[327156-97-8] $C_8H_{17}F_2O_3PS$ (MW 262.25)
InChI = 1/C8H17F2O3PS/c1-6(2)12-14(11,13-7(3)4)8(9,10)15-5/h6-7H,1-5H3
InChIKey = CXJGLDDSOYUAPU-UHFFFAOYAL

(source of phosphonodifluoromethylcarbanion and phosphonodifluoromethyl radical)

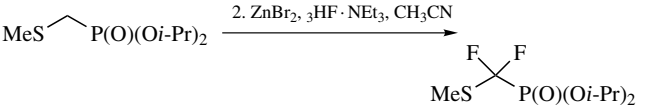
Alternate Names: phosphonic acid, [difluoro(methylthio)-methyl]-, bis(1-methylethyl) ester.
Physical Data: bp 66–72 °C at 0.8 mmHg, colorless oil.
Solubility: sol in most organic solvents.
Form Supplied in: not commercially available.
Preparative Methods: the reagent is prepared in two steps from diisopropyl methylsulfanylmethylphosphonate.

Preparation. Sodium diisopropylphosphonate generates *S*-methyl diisopropoxyphosphinyldithioformate when treated with carbon disulfide and methyl iodide.[1] The reduction of this compound with sodium borohydride followed by trapping of the thiolate with methyl iodide leads to diisopropyl methylsulfanylmethylphosphonate(eq 1).[2]



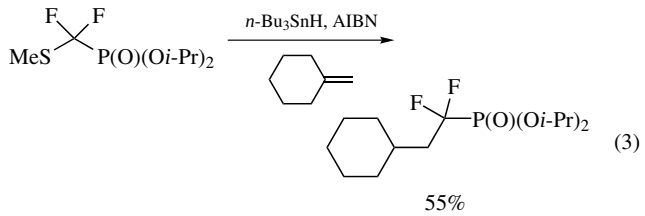
(1)

The phosphonate is then converted into diisopropyl methylsulfanyldichloromethylphosphonate upon treatment with sulfuryl chloride[3] or *N*-chlorosuccinimide[4] and the latter is treated with hydrogen fluoride/triethylamine/zinc bromide to afford diisopropyl methylsulfanyldifluoromethylphosphonate (eq 2).

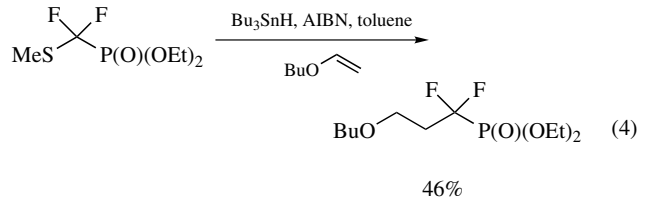


(2)

Radical Addition to Alkenes. Diisopropyl methylsulfanyldifluoromethylphosphonate is a precursor of phosphonodifluoromethyl radicals. The radical addition product is generated when diisopropyl methylsulfanyldifluoromethylphosphonate is treated with tributyltin hydride in the presence of *AIBN* (eq 3).[5] A similar reaction is also observed with the analogous diethyl methylsulfanyldifluoromethylphosphonate (eq 4).

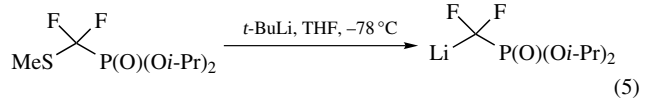


(3)



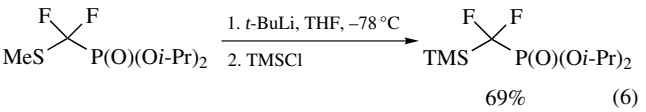
(4)

1,2-Additions. Diisopropyl methylsulfanyldifluoromethylphosphonate is a precursor of phosphonodifluoromethyl carbanion. Treatment of the phosphonate with *tert*-BuLi in THF at −78 °C leads to the formation of lithium diisopropyl difluoromethylphosphonate (eq 5).[6]

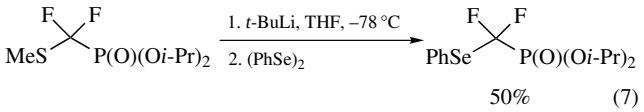


(5)

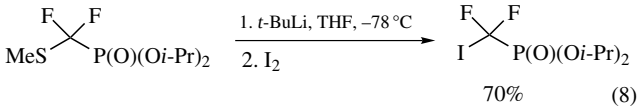
This anion can be trapped with a wide range of electrophiles such as trimethylsilyl chloride (eq 6), diphenyl disulfide or diselenide (eq 7), and iodine (eq 8).



(6)

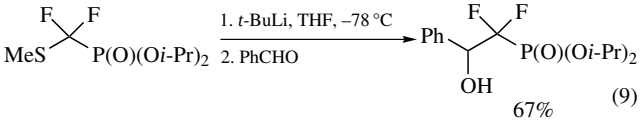


(7)

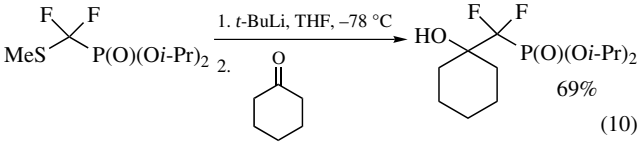


(8)

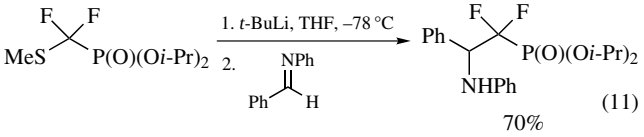
Moreover, this anion undergoes efficient 1,2-addition reactions with aldehydes (eq 9), ketones (eq 10), imines (eq 11), esters (eq 12), carbon disulfide (eq 13), and DMF (eq 14).



(9)



(10)



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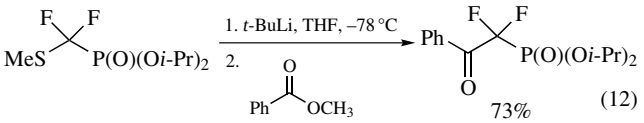
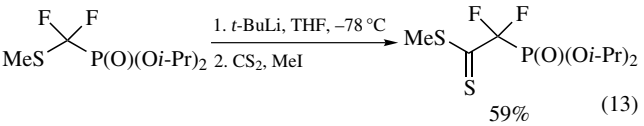
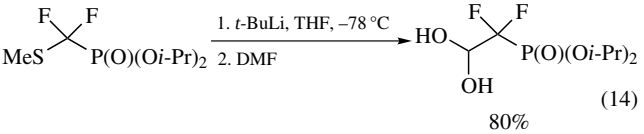


(12)

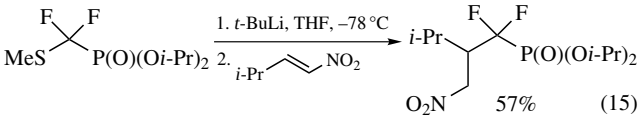


(13)



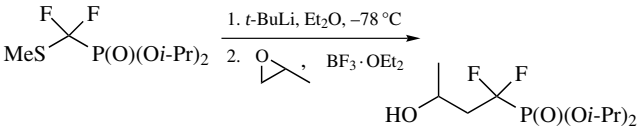
(14)

Conjugate Additions. Lithium phosphonodifluoromethyl undergoes conjugate addition reactions with α,β-unsaturated nitro derivatives (eq 15).[6]

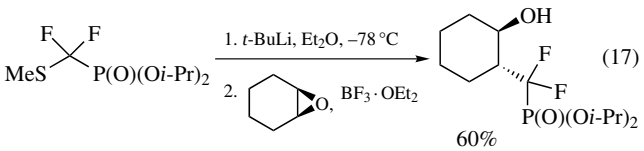


(15)

Opening of Cyclic Ethers. This anion is sufficiently nucleophilic to open epoxides in the presence of boron trifluoride etherate (eqs 16–17).[7]

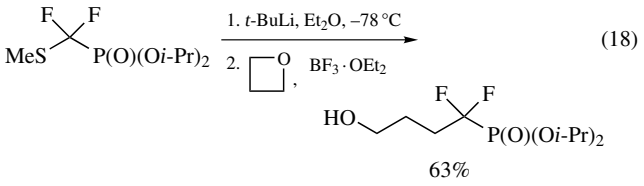


(16)



(17)

Furthermore, the opening reactions of oxetane and tetrahydrofuran proceed nicely under these reaction conditions to give primarily the corresponding alcohols (eqs 18 and 19).



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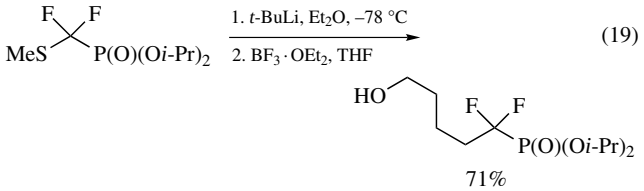

(19)

1. Grisley, D. W., *J. Org. Chem.* **1961**, *26*, 2544.
2. Makomoto, H.; Masson, S.; Saquet, M., *Tetrahedron* **1994**, *50*, 10277.
3. Mikolajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B.; Midura, W., *J. Org. Chem.* **1978**, *43*, 2518.
4. Fild, M.; Vahldiek, M., *Phosphorus Sulfur* **1988**, *40*, 207.
5. Lequeux, T.; Lebouc, F.; Lopin, C.; Yang, H.; Gouhier, G.; Piettre, S. R., *Org. Lett.* **2001**, *3*, 185.
6. Henry-dit-Quesnel, A.; Toupet, L.; Pommelet, J.-C.; Lequeux, T., *Org. Biomol. Chem.* **2003**, *1*, 2486.
7. Ozouf, P.; Binot, G.; Pommelet, J.-C.; Lequeux, T. P., *Org. Lett.* **2004**, *6*, 3747.

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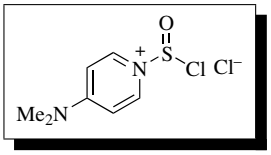
4-(Dimethylamino)pyridinium Chlorosulfite Chloride



[86128-91-8] $C_7H_{10}Cl_2N_2OS$ (MW 241.16)

InChI = 1/C7H10ClN2OS.ClH/c1-9(2)7-3-5-10(6-4-7)12(8)11;/h3-6H,1-2H3;1H/q+1;/p-1/fC7H10ClN2OS.Cl/h;1h/qm;-1

InChIKey = UKNRZUCJDJOKJP-DPSUKLAQCE

(synthesis of esters and amides from carboxylic acids; dehydration of aldoximes; synthesis of chlorosilanes)

Physical Data: mp 155–157 °C.

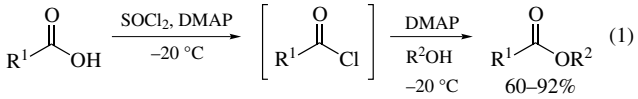
Solubility: sol CH_2Cl_2.

Preparative Methods: generated by reaction of 4-dimethylaminopyridine with thionyl chloride in CH_2Cl_2 at −20 °C and isolated as a solid. The reagent is most commonly prepared and used in situ.[1]

Purification: need not be isolated; no methods have been described for its purification.

Handling, Storage, and Precautions: must be assumed to be moisture sensitive; precautions should be taken in accordance with those advised for both DMAP and $SOCl_2$.

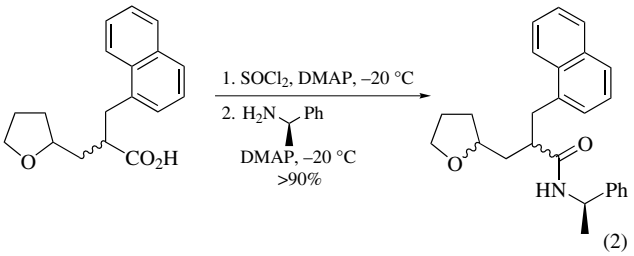
Carboxyl Activation: Synthesis of Esters and Amides from Carboxylic Acids. 4-(Dimethylamino)pyridinium chlorosulfite chloride is more reactive than either thionyl chloride or thionyl chloride/pyridine for carboxyl activation. Aliphatic and aromatic, as well as amino acids (in racemic form), undergo activation (via the acyl halide) and subsequent esterification by reaction with an alcohol at −20 °C (eq 1).[1] The esterification step requires the addition of a second equivalent of DMAP and this method has been applied to a range of functionalized carboxylic acids.



(1)

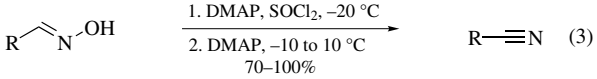
High yields of esters are obtained from both acid-sensitive (cyanoacetic acid) and base-sensitive carboxylic acids (3-phenylpropionic acid and trichloroacetic acid) and, in these latter cases, use of 4-(dimethylamino)pyridinium chlorosulfite chloride is much more effective than use of thionyl chloride alone. The esterification process has been claimed to be independent of the steric environment of the carboxyl function, though this reagent may be of more limited value with heavily substituted benzoic acids.[2]

Carboxyl activation, in the presence of a primary amine, leads to the corresponding amide in excellent yield (eq 2).[3] In both the esterification and amidation processes and the oxime dehydration reaction discussed below, recovery of DMAP is straightforward.



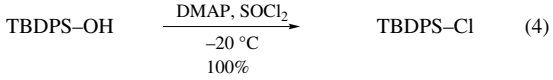
(2)

Dehydration of Aldoximes. A range of alkyl, aryl, and heteroaryl aldoximes undergo smooth dehydration with 4-(dimethylamino)pyridinium chlorosulfite chloride at −10 to +10 °C to give the corresponding nitriles in 70–100% yield (eq 3).[4]



(3)

Synthesis of Chlorosilanes. *t*-Butyldiphenylsilanol has been converted to the corresponding chlorosilane in quantitative yield using 4-(dimethylamino)pyridinium chlorosulfite chloride (eq 4).[5] The use of oxalyl chloride/DMAP is also highly effective for this transformation, but a number of other reagents (concentrated HCl; MeCOCl; $SOCl_2$; *o*-phenylene cyclohexylphosphorochlorimidate/SO_2Cl_2) either fail completely or give inferior yields of product.



(4)

1. Arrieta, A.; García, T.; Palomo, C., *Synth. Commun.* **1982**, *12*, 1139.
2. Jütten, P.; Dornhagen, J.; Scharf, H.-D., *Tetrahedron* **1987**, *43*, 4133.
3. Descours, D.; Festal, D.; Leger, J.-M.; Carpy, A., *Helv. Chim. Acta* **1991**, *74*, 1757.
4. Arrieta, A.; Palomo, C., *Synthesis* **1983**, 472.
5. Mullen, D. G.; Barany, G., *J. Org. Chem.* **1988**, *53*, 5240.

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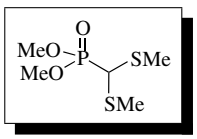
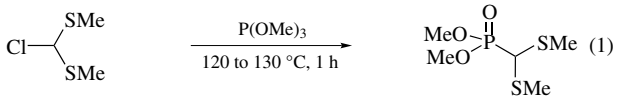
Dimethyl Bis(methylthio)methylphosphonate[1]



[61779-87-1] $C_5H_{13}O_3PS_2$ (MW 216.29)
InChI = 1/C5H13O3PS2/c1-7-9(6,8-2)5(10-3)11-4/h5H,1-4H3
InChIKey = CAHXAVHWMLFWIT-UHFFFAOYAG

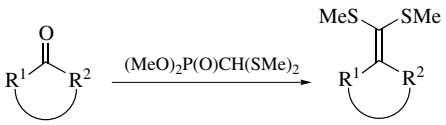
(treatment with base gives a carbanion that reacts with aldehydes and ketones[1–5])

Alternate Name: *O,O*-dimethyl formylphosphonate *S,S*-dimethyl thioacetal.
Physical Data: bp 72 °C/0.05 mmHg.
Solubility: sol THF, DME.
Form Supplied in: not commercially available.
Preparative Methods: $(MeO)_2P(O)CH(SMe)_2$[6] and related *S,S*-thioacetals of formylphosphonates[6,7] are readily prepared in high yields by the Arbuzov reaction of trialkyl phosphites with chloro dithioacetals (eq 1).[1,8] Other syntheses of thiophosphonates are known.[9]

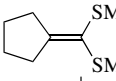
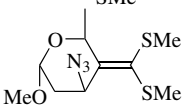


(1)

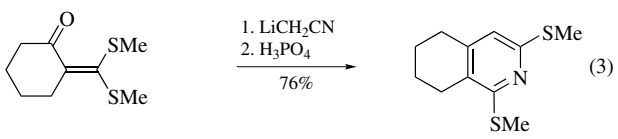
Reactions with Aldehydes and Ketones. The carbanion derived from the treatment of $(MeO)_2P(O)CH(SMe)_2$ with a base reacts with cyclic and acyclic, aliphatic and aromatic aldehydes and ketones in a Horner–Wadsworth–Emmons reaction to give ketene *S,S*-thioacetals in high yields[1–5] (eq 2[2,3]). The carbanion is generated using either butyllithium in THF at −78 °C[2,3] or, less commonly, sodium hydride in DME.[2] Alternatively, with aromatic aldehydes the reaction may be performed under two-phase conditions using benzyltriethylammonium chloride (TEBA) as a phase-transfer catalyst.[2]



(2)

Product	Conditions	Yield (%)	Ref
$H_2C{=}CH(SMe)_2$	BuLi, THF, –78 °C	96	2
$Me_2C{=}CH(SMe)_2$	BuLi, THF, –78 °C	80	2
$PhHC{=}CH(SMe)_2$	BuLi, THF, –78 °C	90	2
	NaH, DME	75	
	50% NaOH, THF, 5% TEBA	88	
	BuLi, THF, –78 °C	82	2
	BuLi, THF, –78 °C	60	3

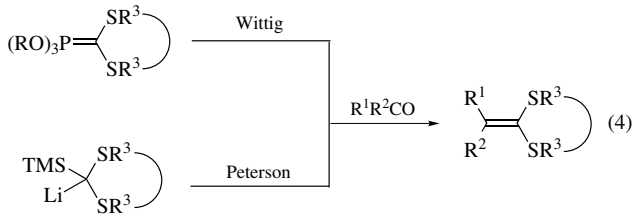
Ketene *S,S*-thioacetals are key synthetic intermediates, susceptible to nucleophilic and electrophilic attack.[1,2b,10] Hydrolysis and alcoholysis of ketene *S,S*-thioacetals yields carboxylic acids and esters, respectively. Other transformations of ketene *S,S*-thioacetals allow homologation of the precursor carbonyl compound and polyfunctional ketene *S,S*-thioacetals provide access to heterocycles (e.g. eq 3).[11]



(3)

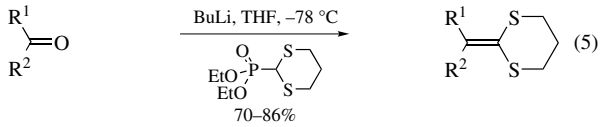
Alternative methods for the preparation of ketene *S,S*-thioacetals from carbonyl compounds include the Wittig reaction with

phosphite ylides and the Peterson reaction with lithium derivatives of trimethylsilyl dithioacetals (eq 4).[1] The Wittig preparation is limited to aldehydes and is further restricted by the availability of the phosphite ylides. Also, whereas the phosphate ester byproduct of the Horner–Wadsworth–Emmons reaction is water soluble and therefore easily separated from the ketene *S,S*-thioacetal, the phosphine oxide byproduct of the Wittig reaction is usually of a solubility similar to the product. The Peterson alkenation is a general synthesis, but suffers long reaction times and low yields with sterically hindered ketones.



(4)

Related Systems. The carbanions of related *S,S*-thioacetals of formylphosphonates also react with aldehydes and ketones, including α,β-unsaturated aldehydes and ketones, to give the corresponding ketene *S,S*-thioacetals[2,4,5,12] (e.g. eq 5[2,12]). Horner–Wadsworth–Emmons reactions of carbonyl compounds with *O,S*-thioacetals of formylphosphonates[2a,5] [e.g. $(MeO)_2P(O)CH$-$(SMe)OMe$] and mono(thio)phosphonates[4,13] [e.g. $(MeO)_2P(O)$-CH_2SMe] are also known.



70–86%

(5)

1. (a) Kolb, M. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: Chichester, 1980; Part 2, p 669 and refs therein. (b) Kolb, M., *Synthesis* **1990**, 171 and refs therein.
2. (a) Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A.; Mlotkowska, B., *Tetrahedron Lett.* **1976**, 2731. (b) Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A.; Mlotkowska, B.; Gross, H.; Costisella, B., *Tetrahedron* **1978**, *34*, 3081.
3. Hanessian, S.; Desilets, D.; Rancourt, G.; Fortin, R., *Can. J. Chem.* **1982**, *60*, 2292.
4. Martin, S. F., *Synthesis* **1979**, 633 and refs therein.
5. Cherkasov, R. A.; Kutyrev, G. A.; Pudovik, A. N., *Tetrahedron* **1985**, *41*, 2567 and refs therein.
6. Mlotkowska, B.; Gross, H.; Costisella, B.; Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A., *J. Prakt. Chem.* **1977**, *319*, 17.
7. Gross, H.; Keitel, I.; Costisella, B., *J. Prakt. Chem.* **1978**, *320*, 255.
8. (a) Shahak, I.; Almog, J., *Synthesis* **1969**, 170. (b) McGuire, H. M.; Odom, H. C., Jr.; Pinder, A. R., *J. Chem. Soc., Perkin Trans. 1* **1974**, 1879.
9. (a) Ishikawa, K.; Akiba, K.; Inamoto, N., *Tetrahedron Lett.* **1976**, 3695. (b) Gross, H.; Costisella, B. S. **1977**, 622. (c) Mikolajczyk, M.; Grzejszczak, S.; Chefczynska, A.; Zatorski, A., *J. Org. Chem.* **1979**, *44*, 2967.
10. Gröbel, B.-T.; Seebach, D., *Synthesis* **1977**, 357.
11. Gupta, A. K.; Ila, H.; Junjappa, H., *Tetrahedron Lett.* **1988**, *29*, 6633.
12. Mikolajczyk, M.; Balczewski, P., *Tetrahedron* **1992**, *48*, 8697.
13. Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A., *Synthesis* **1975**, 278.

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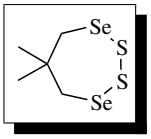
6,6-Dimethyl-1,4-diseleno-3,7-tetrasulfide



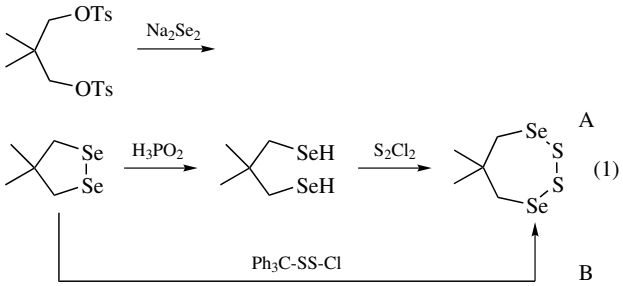
[110027-90-2] $C_5H_{10}S_2Se_2$ (MW 292.18)
InChI = 1/C5H10S2Se2/c1-5(2)3-8-6-7-9-4-5/h3-4H2,1-2H3
InChIKey = WILGRFWQSZSXML-UHFFFAOYAJ

(reagent used to sulfurate dienes with thermally generated diatomic sulfur)

Physical Data: mp 50–51 °C; yellow solid.
Solubility: benzene, toluene, and acetone.
Purification: column chromatography on silica gel.
Handling, Storage, and Precautions: to help prevent decomposition during extended storage, the reagent should be kept under a nitrogen atmosphere and refrigerated at ∼ −15 °C. No data on toxicity. Incompatible with oxidizing agents.

Preparation. Currently two methods exist to prepare 6,6-dimethyl-1,4-diseleno-3,7-tetrasulfide.

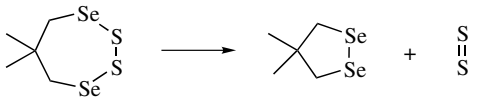
The original method (A) involves conversion of the bis-tosylate to the cyclic diselenide followed by reduction of the Se–Se bond and ring closure with sulfur monochloride (eq 1).[1] This method was recently improved in both yield and simplicity using a sulfur insertion methodology (path B, eq 1).[2]



(1)

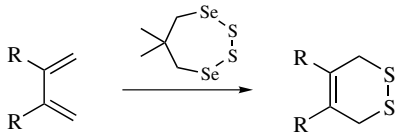
First Storable Source of Diatomic Sulfur S_2. Access to diatomic sulfur (a very reactive sulfur species) was limited to methods involving decomposition of reactive intermediates like triphenylphosphane ozonide[3] or bis(thiobenzoyl)biphenyl[4] (generated in situ from BCl_3 and 2,2′-dibenzoylbiphenyl). Their spontaneous decomposition produced the 2-sulfur-transfer reagent. The inconveniencies of this approach lead to a series of ingenious

inventions.[5] The Se-SS-Se moiety allowed for the first stoichiometric, storable source of diatomic sulfur that could be used to transfer sulfur to dienes under thermal conditions (eq 2, refluxing the compound in chlorobenzene for up to 4 h). The temperature of the transfer is an important factor as in refluxing toluene, the diatomic sulfur extrusion is complete only after 6 days.



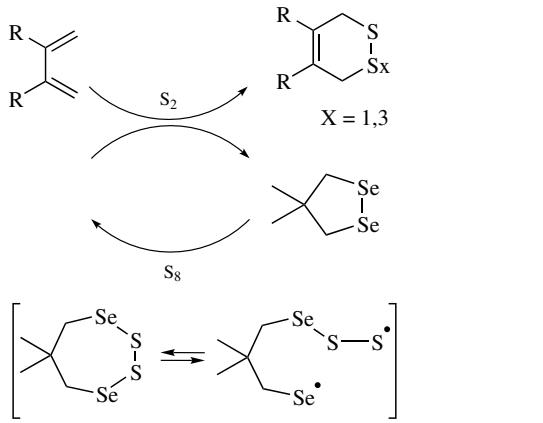
(2)

Sulfur Transfer. Schmidt and Görl reported a successful application of 5,5-dimethyl-1,2-dithia-3,7-diselenacycloheptane in the sulfuration of dienes. The diatomic sulfur species liberated under thermal conditions by the contraction of the diselenotetrasulfide ring reacted efficiently with several dienes (eq 3). The product disulfides have been obtained from 40% yield for myrcene up to 54% for 2,3-diphenylbutadiene. Apparently, the reaction has its applicability limited to products that have no tendency to aromatize (cyclohexadiene and substituted cyclopentadiene derivatives) or polymerize (cyclopentadiene).



(3)

Recently, sulfur transfer to dienes using 6,6-dimethyl-1,4-diseleno-3,7-tetrasulfide and other diselenotetrasulfides was reinvestigated.[6] It is not even necessary to use diselenotetrasulfides as actual reagents. Indeed, they form in the reaction medium from the corresponding diselenides with an excess of elemental sulfur (eq 4). Under the thermal conditions required for efficient sulfur transfers, a homolytic cleavage of the Se–S bond results in generation of active sulfur species delivering sulfur to dienes.



(4)

In comparison with acyclic (phenyl and benzyl) diselenotetrasulfides, 6,6-dimethyl-1,4-diseleno-3,7-tetrasulfide gives cleaner sulfur-transfer products (both di- and tetrasulfides[7]) although the yields are comparable. Clean sulfur transfer is advantageous as some of the reaction side products, especially polymers and selenide adducts, are difficult to remove from the reaction mixture.

Related Reagents. Diselenides, Phenyl Diselenotetrasulfides Benzyl Diselenotetrasulfides, Dialkoxydisulfides.

1. Schmidt, M.; Görl, U., *Angew. Chem., Int. Ed.* **1987**, *25*, 887.
2. Rys, A. Z.; Harpp, D. N., *Tetrahedron Lett.* **2000**, *41*, 7169.
3. Steliou, K.; Gareau, Y.; Harpp, D. N., *J. Am. Chem. Soc.* **1984**, *106*, 799.
4. Steliou, K.; Salama, P.; Brodeur, D.; Gareau, Y., *J. Am. Chem. Soc.* **1987**, *109*, 926.
5. Steliou, K., *Acc. Chem. Res.* **1991**, *24*, 341; Harpp, D. N., *Phosphorus, Sulfur, Silicon Relat. Elem.* **1997**, *120*, 41; Tardif, S. L.; Rys, A. Z.; Abrams, C. B.; Abu-Yousef, I. A.; Leste-Lasserre, P. B. F.; Schultz, E. K. V.; Harpp, D. N., *Tetrahedron* **1997**, *53*, 12225.
6. Rys, A. Z.; Hou, Y.; Abu-Yousef, I. A.; Harpp, D. N., *Tetrahedron Lett.* **2004**, *45*, 9181.
7. Tetrasulfides are easily converted to disulfides when treated with triphenylphosphine (Rys, A. Z.; Harpp, D. N., *Tetrahedron Lett.* **1997**, *38*, 4931).

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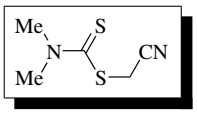
McGill University, Montréal, Québec, Canada

N,N-Dimethyldithiocarbamoylacetonitrile[1]

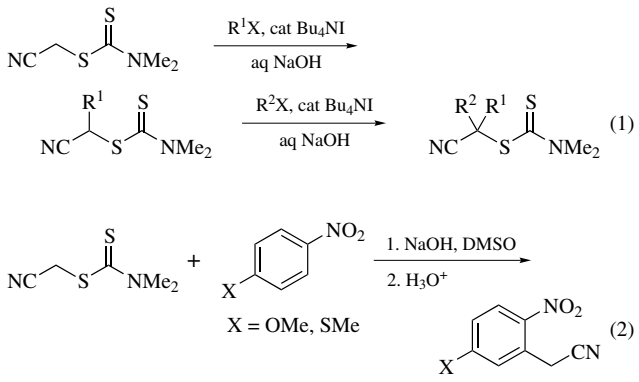


[61540-35-0] $C_5H_8N_2S_2$ (MW 160.29)
InChI = 1/C5H8N2S2/c1-7(2)5(8)9-4-3-6/h4H2,1-2H3
InChIKey = LVCZXSPJNILIPO-UHFFFAOYAG

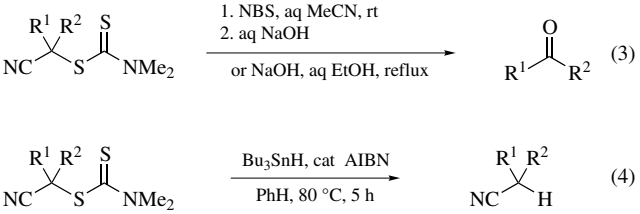
(alkylation;[2] arylation;[3] transformation to other functional groups;[2,4] reductive desulfurization[3,5])

Physical Data: mp 73–74 °C.
Solubility: insol H_2O; sol THF, dichloromethane, DMF; slightly sol alcohol.
Form Supplied in: white crystalline solid.
Preparative Method: quantitatively prepared from chloroacetonitrile and sodium *N,N*-dimethyldithiocarbamate at rt in methanol.
Purification: recrystallized from ethanol.
Handling, Storage, and Precautions: can be used and be stored at rt under air. Use in a fume hood.

Nucleophilic Substitutions. *N,N*-Dimethyldithiocarbamoylacetonitrile (**1**) serves as an active methylene compound, because its carbanion is stabilized by sulfur and cyano groups. It can be alkylated stepwise in aqueous sodium hydroxide under phase transfer catalysis (eq 1).[2] The anion undergoes nucleophilic aromatic substitution to give nitroarenes, with elimination of the dithiocarbamate group (eq 2).[3] Nucleophilic addition of (**1**) to phenyl isothiocyanate also occurs readily.[6]



Transformations. Dialkylated *N*,*N*-dimethyldithiocarbamoylacetonitriles are transformed into ketones by *N*-bromosuccinimide bromination or by basic hydrolysis (eq 3),[2] and they are hydrolyzed in acidic ethanol to produce α-mercapto carboxylates.[4] Bromination of (**1**) in methanol leads to the formation of 1,3-dithietan-2-ylium ion.[7] Alkylated *N*,*N*-dimethyldithiocarbamoylacetonitriles are reductively desulfurized to α-branched nitriles with tributylstannane in the presence of a catalytic amount of azobisisobutyronitrile (eq 4).[5]



Related Reagents. *N*,*N*-Diethylaminoacetonitrile; 2-(2,6-Dimethylpiperidino)acetonitrile; Lithioacetonitrile; Methoxyacetonitrile

1. (a) Jensen, K. A., *J. Prakt. Chem.* **1941**, *159*, 189(b) Nachmias, G., *Ann. China. (Rome)* **1952**, *7*, 584 (*Chem. Abstr.* **1954**, *48*, 597).
2. Masuyama, Y.; Ueno, Y.; Okawara, M., *Tetrahedron Lett.* **1976**, 2967.
3. Makosza, M.; Winiarski, J., *J. Org. Chem.* **1984**, *49*, 1494.
4. Masuyama, Y.; Ueno, Y.; Okawara, M., *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3071.
5. Yanagawa, M.; Moriya, O.; Watanabe, Y.; Ueno, Y.; Endo, T., *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2203.
6. Dölling, W.; Vogt, A.; Sperk, K.; Augustin, M., *Synthesis* **1990**, 621.
7. Harris, R. L. N.; McFadden, H. G., *Synthesis* **1985**, 209.

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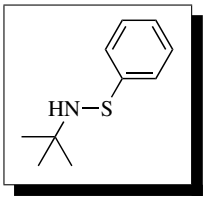
Sophia University, Tokyo, Japan

N-(1,1-Dimethylethyl)benzenesulfenamide



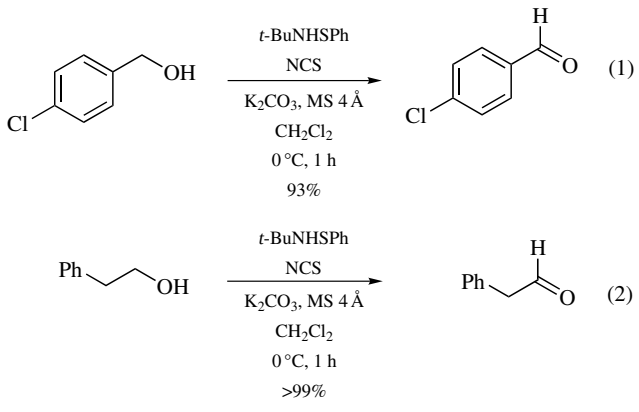
[19117-31-8] $C_{10}H_{15}NS$ (MW 181.30)
InChI = 1/C10H15NS/c1-10(2,3)11-12-9-7-5-4-6-8-9/h4-8,11H,1-3H3
InChIKey = AAQBFMPKCDTAJD-UHFFFAOYAI

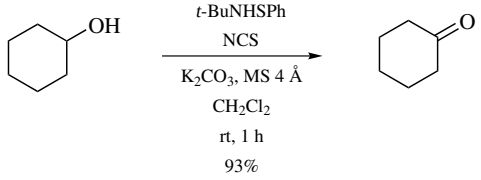
(catalyst used for the oxidation of alcohols to aldehydes and ketones)

Physical Data: bp 94–95 °C/7 mmHg.
Solubility: soluble in most organic solvents.
Form Supplied in: colorless oil.
Analysis of Reagent Purity: NMR, IR.
Preparative Methods: commercially available or prepared by reacting *tert*-butylamine with benzenesulfenyl chloride in ether.
Purification: distillation at 94–95 °C/7 mmHg.

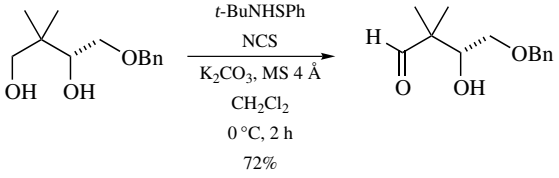
Oxidation of Alcohols. *N*-(1,1-Dimethylethyl)benzenesulfenamide is most commonly used as a catalyst for the oxidation of alcohols to aldehydes and ketones.[1] The reaction requires the use of stoichiometric amounts of *N*-chlorosuccinimide (NCS) in order to convert the sulfenamide to the corresponding sulfinimidoyl chloride, which is the active oxidant in the reaction. In addition, it is necessary to perform the reaction in the presence of a base, most commonly potassium carbonate, in order to trap the HCl that is formed. The yield of the reaction is improved by the presence of a dehydrating agent, usually molecular sieves (MS). The preferred solvent for the reaction is dichloromethane.

This oxidation is extremely facile and generally provides the aldehydes or ketones in >90% yield after 1 h. Oxidations of allylic and benzylic alcohols occur at 0 °C (eq 1) and other primary and secondary alcohols are oxidized between 0 °C to room temperature (eqs 2 and 3). Oxidation of the product aldehyde to the carboxylic acid is not observed. In addition, this method can be used to selectively oxidize the primary alcohol of a diol to provide the corresponding hydroxyaldehyde (eq 4). This method has been used to oxidize alcohols on a preparative scale (>100 g).



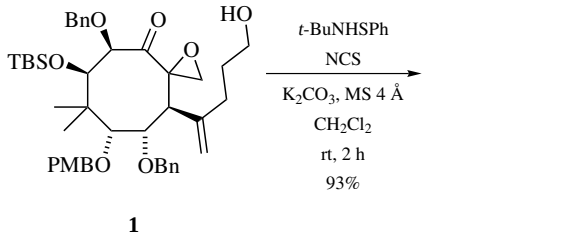


(3)

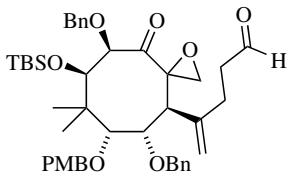


(4)

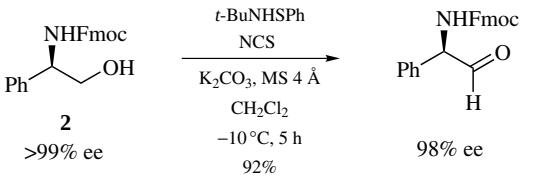
The oxidation of alcohols with *N*-(1,1-dimethylethyl)benzenesulfenamide is extremely mild and many sensitive functional groups such as epoxides and alkenes are tolerated by the reaction conditions (eq 5). In the case of alcohol **1**, oxidation with tetrapropylammonium perruthenate (TPAP) resulted in only 58% yield and Swern oxidation was unsuccessful.[1,2] Epimerizable aldehydes such as the protected phenylglycinol **2** do not undergo racemization when oxidized (eq 6).[1]



1



(5)

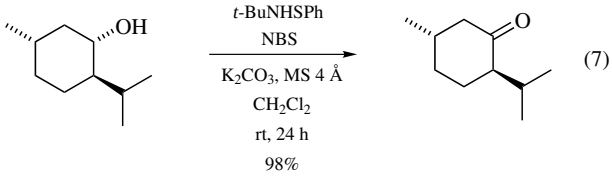


2
>99% ee

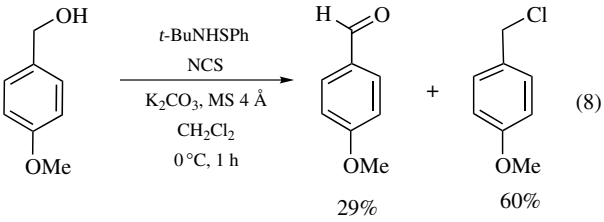
98% ee

(6)

In some cases, oxidations of sterically hindered alcohols were slow under the standard conditions. However, by extending the reaction times and using *N*-bromosuccinimide instead of NCS, excellent yields of the ketone could still be obtained (eq 7).[1] Also, alcohols which can form stabilized carbocations provide the aldehyde in low yields under the standard conditions (eq 8). In this case, the major product is the alkyl chloride. By using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base instead of potassium carbonate, good yields of the aldehyde can be obtained (eq 9).



(7)



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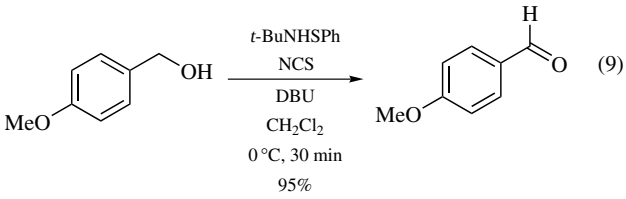
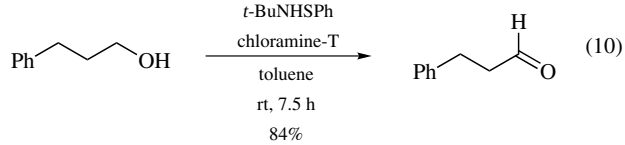


(9)

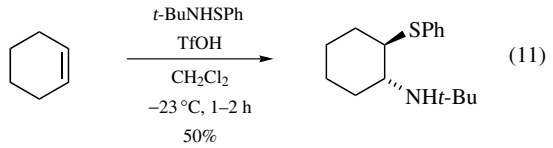
As mentioned above, the active oxidant in this reaction is *N*-(1,1-dimethylethyl)benzenesulfinimidoyl chloride, and alcohols can be oxidized to the carbonyl compounds using stoichiometric amounts of this compound.[3] However, *N*-(1,1-dimethylethyl)benzenesulfenamide and other by-products of the oxidation can be difficult to separate from the desired aldehyde or ketone, so it is generally advantageous to use the catalytic method.

An alternative chlorinating agent, chloramine-T, has also been used with *N*-(1,1-dimethylethyl)benzenesulfenamide for the oxidation of alcohols to aldehydes (eq 10).[4] The chloramine-T acts as the base as well as the chlorinating agent, so there is no need for an added base. Dehydrating additives are also not necessary under these conditions. Another advantage is that the *p*-toluenesulfonamide by-product is easily separated from the product and can be converted back into chloramine-T. However, yields of product when using chloramine-T are generally lower and reaction times are longer than with NCS.

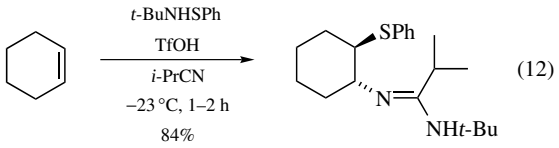


(10)

Aminosulfenation and Amidinosulfenation of Alkenes. There is one report of using *N*-(1,1-dimethylethyl)benzenesulfenamide to convert an alkene to the amino thioether (eq 11).[5] The sulfenamide reacts with the alkene in dichloromethane in the presence of trifluoromethanesulfonic acid at −23 °C. If a nitrile is used as the solvent instead of dichloromethane, the amidino thioether is obtained in good yield (eq 12).

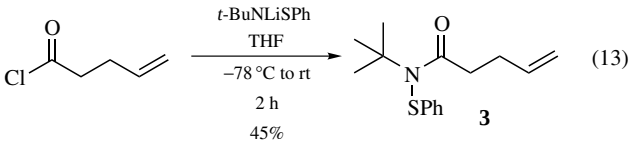


(11)



(12)

Preparation of Amidyl Radicals from Acid Chlorides. The anion of *N*-(1,1-dimethylethyl)benzenesulfenamide can be prepared upon treatment with *n*-butyllithium and reacts with an acid chloride to provide the *N*-phenylthioamide **3** (eq 13).[6] An amidyl radical derived from compound **3** can be formed by homolytic cleavage of the N–S bond.



(13)

Related Reagents. *N*-Bromosuccinimide; Chloramine-T; *N*-Chlorosuccinimide; *N*-(1,1-Dimethylethyl)benzenesulfinimidoyl Chloride; Tetrapropylammonium Perruthenate; Dimethyl sulfoxide-oxalyl Chloride; 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 2-Iodoxybenzoic Acid (IBX); Diphenyl Sulfoxide.

1. Matsuo, J.-I.; Iida, D.; Yamanaka, H.; Mukaiyama, T., *Tetrahedron* **2003**, *59*, 6739.
2. Ogawa, Y.; Kuroda, K.; Matsuo, J.-I.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **2005**, *78*, 677.
3. Matsuo, J.-I.; Iida, D.; Tatani, K.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **2002**, *75*, 223.
4. Kitagawa, H.; Mukaiyama, T., *Chem. Pharm. Bull.* **2002**, *50*, 1276.
5. Brownbridge, P., *Tetrahedron Lett.* **1984**, *25*, 3759.
6. Chen, Q.; Shen, M.; Tang, Y.; Li, C., *Org. Lett.* **2005**, *7*, 1625.

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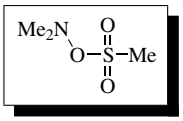
N,N-Dimethyl-*O*-(methylsulfonyl)-hydroxylamine[1]



[75812-61-2] $C_3H_9NO_3S$ (MW 139.20)
InChI = 1/C3H9NO3S/c1-4(2)7-8(3,5)6/h1-3H3
InChIKey = UIANJNAHYLTTOQ-UHFFFAOYAW

(reagent for electrophilic aminations, Me_2N transfers to nucleophiles)

Physical Data: mp 33–35 °C.[2]

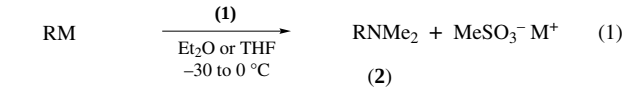
Solubility: sol THF, diethyl ether; very sol $CHCl_3$, CH_2Cl_2.[2]

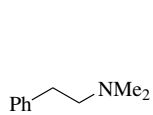
Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) (ppm) 2.90 (s, 6 H, Me_2N), 3.08 (s, 3 H, $MeSO_2$).[2]

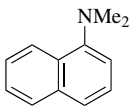
Preparative Methods: to a solution of 29.3 g (300 mmol) *N,N*-dimethylhydroxylamine hydrochloride and 35.6 g (300 mmol) methanesulfonyl chloride in 360 mL CH_2Cl_2 is added dropwise under stirring at −20 °C a solution of 60.7 g (600 mmol) triethylamine in 240 mL CH_2Cl_2. After stirring for 30 min at 0 °C the reaction mixture is poured into ice water, the organic phase is extracted another two times with ice water and then dried over $MgSO_4$ at 0 °C. After removal of the solvent at 0 °C the noncrystalline residue is dissolved in 60 mL diethyl ether. On standing at −30 °C, *N,N*-dimethyl-*O*-(methylsulfonyl)hydroxylamine (**1**) crystallizes in colorless needles which are separated in a cooled frit. After one (or two) recrystallization(s) from diethyl ether between 21.9 and 26.4 g (53–63%) (**1**) are isolated.[3,4] In a similar fashion the following compounds have been prepared and used in electrophilic amination reactions: *N,N*-dimethyl-*O*-(phenylsulfonyl)hydroxylamine, mp 18–19 °C;[2b,3] *N,N*-diethyl-*O*-(mesitylsulfonyl)hydroxylamine, mp 103–104 °C;[2b,3] *N,N*-diethyl-*O*-(phenylsulfonyl)hydroxylamine, mp 46–47 °C;[2b] *N,N*-diethyl-*O*-(mesitylsulfonyl)hydroxylamine, mp 68–69 °C;[2b,3] *N*-(*O*-phenylsulfonyl)hydroxypiperidine, mp 57–58 °C;[2b] *N*-(*O*-mesitylsulfonyl)hydroxypiperidine, mp 50–51 °C;[2b] *N*-(*O*-mesitylsulfonyl)hydroxypyrrolidine, mp 23–24 °C.[2b]

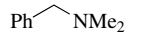
Handling, Storage, and Precautions: reagents for electrophilic aminations with *N,N*-dimethyl(dialkyl) functionality like (**1**) are much more stable than their NH_2 analogs. Thus the pure compound (**1**) can be stored at −30 °C for at least 1 year.[2,3] Impure (**1**) (and related compounds), however, may decompose at rt,[2,3] as also reported for *N,N*-diethyl-*O*-(mesitylsulfonyl)hydroxylamine.[5]

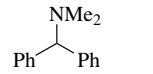
Electrophilic Aminations. *N,N*-Dimethyl-*O*-(methylsulfonyl) hydroxylamine (**1**) reacts with organometallic compounds RM to give *N,N*-dimethylamines (**2**) (eq 1). *N,N*-Dimethylamines prepared via eq 1 from RM and (**1**) together with a specification of RM are shown in (**3**)–(**19**).

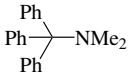


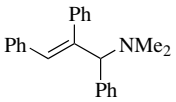

(**3**) 70% (RMgBr)

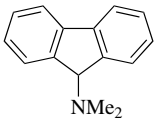

(**4**) 50% (RMgBr)

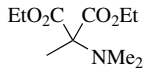

(**5**) 43% (RMgCl)

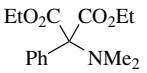

(**6**) 84% (RLi)

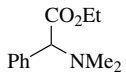

(**7**) 60% (RLi)

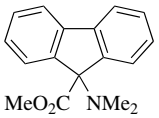

(**8**) 31% (RLi)

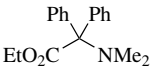

(**9**) 61% (RLi)

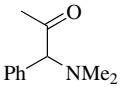

(**10**) 50% (RNa)
50% (RLi)

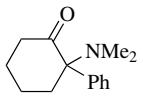

(**11**) 52% (RLi)
39% (RNa)

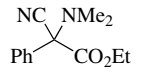

(**12**) 48% (RLi)

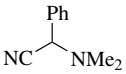

(**13**) 54% (RNa)

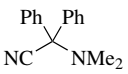

(**14**) 34% (RLi)


(**15**) 52% (RLi)


(**16**) 50% (RLi)

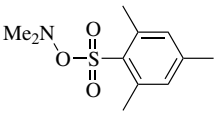

(**17**) 95% (RLi)

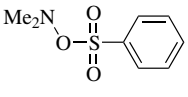

(**18**) 69% (RLi)

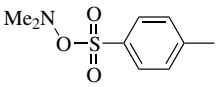

(**19**) 67% (RLi)

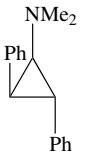
As can be seen from the structures shown, *N,N*-dimethyl-*O*-(methylsulfonyl)hydroxylamine (**1**) aminates alkyl Grignard compounds (to give **3**) and aryl Grignard compounds (to give **4**) with moderate yields. The same is true for 'benzylic anion' type carbon atoms (**5**–**9**). Compounds (**10**) and (**11**) are formed from the corresponding malonates, while (**12**)–(**16**) are derived from (ester)enolates, although with aryl-stabilized anionic carbon atoms. Metalated cyanides lead to (**17**)–(**19**).

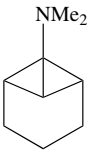
Related amination reactions of organometallic compounds RM have been performed with *N,N*-dimethyl-*O*-(mesitylsulfonyl)hydroxylamine (**20**),[3] *N,N*-dimethyl-*O*-(phenylsulfonyl)hydroxylamine (**21**),[3] and *N,N*-dimethyl-*O*-(*p*-tolylsulfonyl)hydroxylamine (**22**).[4a] Structures (**23**)–(**26**) provide examples of *N,N*-dimethylamines formed by reactions of RM with the mesitylsulfonyl species (**20**).[3,6]

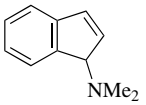

(**20**)

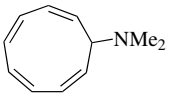

(**21**)


(**22**)

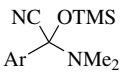

(**23**) 47% (RMgBr)

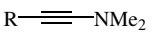

(**24**) 54% (RLi)

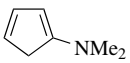

(**25**) 57% (RLi)


(**26**) 69% (RLi)

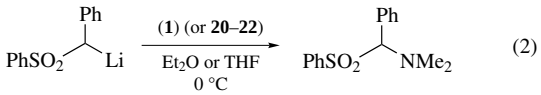
N,N-Dimethylamines of strained hydrocarbons like (**23**) and especially (**24**) are otherwise not easily accessible. The same is true for the cyclononatetraenylamine (**26**).[6] *N,N*-Dimethyl-*O*-(*p*-tolylsulfonyl)hydroxylamine (**22**) is reported to react with phenylmagnesium bromide and cyclohexylmagnesium bromide to give the corresponding *N,N*-dimethylamines in 54% and 14% yield, respectively.[4a] For further and comparable electrophilic amination reactions with transfer of a Me_2N group to give, for example, (**27**)–(**29**).


(**27**)

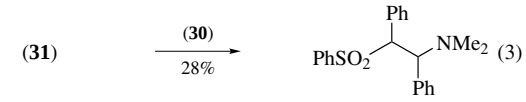

(**28**)


(**29**)

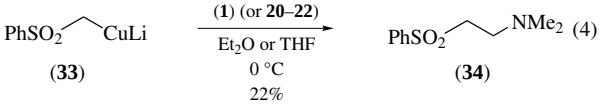
Disadvantages. Normal enolates are not aminated by (**1**), (**20**), (**21**), or (**22**), probably because of a β-elimination of $MeSO_3H$ initiated by deprotonation at one of the *N*-methyl groups.[4a] α-Lithiated sulfones like (**30**) are aminated to give (**31**) (eq 2); however, the reaction does not stop there. Rather, the α-aminosulfone (**31**) leads with unreacted (**30**) to the β-aminosulfone (**32**) (eq 3). Without the phenyl substituent at the anionic carbon atom, only the cuprate (**33**) gives (**34**) (eq 4).[2b]



(**30**) (**31**)

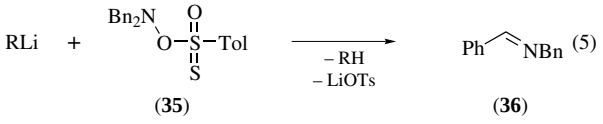


(**32**)



(**33**) (**34**)

The corresponding Li compound deprotonates (**1**) (or **20**–**22**). With the dibenzylamine reagent (**35**), amination of RLi is not observed because of the comparatively fast β-elimination to give (**36**) due to the rather acidic benzylic hydrogen atoms (eq 5).[4b]



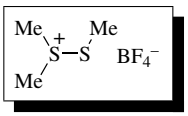
(**35**) (**36**)

Reactions with organometallic compounds in which iodide I^- is present (e.g. in Grignard reagents of the type RMgI) should be avoided because I^- reduces (**1**); a similar reaction is not observed with Cl^- and Br^- containing organometallic compounds.

1. Erdik, E.; Ay, M., *Chem. Rev.* **1989**, *89*, 1947.
2. (a) Nie*β*ner, M., Diploma Thesis, Universität Marburg, 1980. (b) Bernheim, M. Ph. D. Thesis, Universität München, 1981.
3. Boche, G.; Mayer, N.; Bernheim, M.; Wagner, K., *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 687.
4. Other syntheses of *O*-sulfonylhydroxylamines. (a) *N, N*-Dimethyl-*O*-(*p*-tolylsulfonyl)hydroxylamine: Barton, D. H. R.; Bould, L.; Clive, D. L. J.; Magnus, P. D.; Hase, T., *J. Chem. Soc. (C)* **1971**, 2204. (b) *N, N*-Dibenzyl-*O*-(*p*-tolylsulfonyl)hydroxylamine: Sheradsky, T.; Itzhak, N., *J. Chem. Soc., Perkin Trans. 1* **1986**, 13. See also: (c) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M., *J. Org. Chem.* **1973**, *38*, 1239. (d) Carpino, L. A., *J. Am. Chem. Soc.* **1960**, *82*, 3133. (e) Carpino, L. A., *J. Org. Chem.* **1964**, *29*, 2820.
5. Abraham, T.; Curran, D., *Tetrahedron* **1982**, *38*, 1019.
6. Boche, G.; Bernheim, M.; Lawaldt, D.; Ruisinger, B., *Tetrahedron Lett.* **1979**, 4285.

Gernot Boche
Philipps-Universität Marburg, Marburg, Germany

Dimethyl(methylthio)sulfonium Tetrafluoroborate[1]



[5799-67-7] $C_3H_9BF_4S_2$ ((MW 196.07))
InChI = 1/C3H9S2.BF4/c1-4-5(2)3;2-1(3,4)5/h1-3H3;/q+1;-1
InChIKey = LUOOXKXNWLQGLY-UHFFFAOYAV

(electrophilic sulfenylation reagent capable of reacting with nucleophilic atoms;[2] reacts with electron-rich alkenes to promote addition reactions,[3] cyclizations;[4] activates dithioacetals,[5] trithioorthoesters,[6] and thioglycosides[7] for carbon–carbon or carbon–heteroatom bond forming reactions)

Alternate Name: DMTSF.

Physical Data: mp 89–92 °C.

Solubility: soluble in MeCN, $MeNO_2$; insoluble in ether, pet ether; reacts with H_2O and other protic solvents.

Form Supplied in: cream-colored to white solid; available from various suppliers.

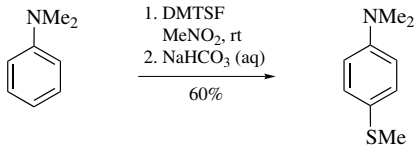
Preparative Method: DMTSF can be conveniently prepared from dimethyl disulfide and trimethyloxonium tetrafluoroborate (Me_3O^+ BF_4^-) in MeCN.[8] Precipitation of the product results after addition of ether and isolation requires filtration under anhydrous conditions.

Handling, Storage, and Precaution: DMTSF must be stored under anhydrous conditions, preferably in a well sealed bottle under nitrogen. Exposure to moisture results in a stench and the reagent is corrosive. Use in a fume hood.

Original Commentary

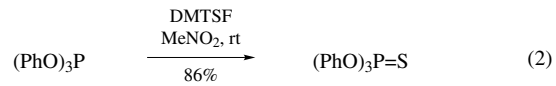
Edward J. Adams
E. I. DuPont de Nemours and Co., Newark, DE, USA

Methylsulfenylation of Nucleophilic Atoms. DMTSF reacts with potassium cyanide to yield MeSCN and with phenylmagnesium bromide to yield thioanisole.[8] Extensive investigations addressed the reactivity of DMTSF with nucleophilic agents.[9] DMTSF does not react with phenol at rt, but reacts slowly at 60 °C to yield the methylthiophenols (*ortho*/*para* = 0.22). The reaction with anisole also requires a temperature of 60 °C and results in *p*-methylthioanisole and *p*-methylthiophenol, a consequence of ether cleavage under the reaction conditions. Unlike phenol, dimethylaniline reacts rapidly with DMTSF at rt, yielding *p*-methylthio-*N,N*-dimethylaniline in 60% yield (eq 1). Despite the presence of an electron-withdrawing group, *p*-nitro-*N,N*-dimethylaniline also reacts rapidly with DMTSF to yield *p*-nitro-*N,N*-dimethyl-*N*-methylthioanilinium tetrafluoroborate.

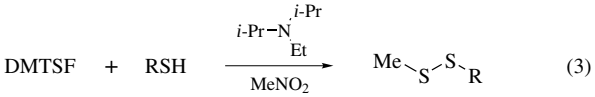


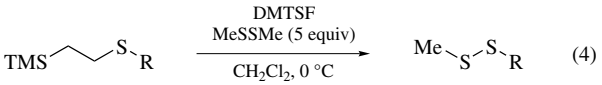
DMTSF reacts rapidly at rt with pyridine to yield the hydrolytically unstable methylthiopyridinium ion, which failed to methylate the MeSMe byproduct. When 4-cyanopyridine was used, an equilibrium mixture was detected by NMR.

Triphenyl phosphite reacts rapidly with DMTSF at rt to yield the methylthiophosphonium salt which, unlike the pyridinium analog, methylates the MeSMe byproduct to yield Me_3S^+ BF_4^-. This salt is removed by precipitation with ether and chromatography provides triphenyl thionophosphate in an 86% yield (eq 2). This technique complements other methods of thionophosphate synthesis from phosphites.[10]



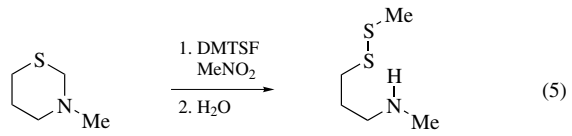
Synthesis of mixed disulfides involving a methylthio unit may utilize DMTSF. Thiols and thiolates react rapidly with the reagent to yield mixed disulfides. Unfortunately, disproportionation occurs, resulting in a mixture of products.[9] Subsequent investigations suggest that the addition of a sterically hindered base (eq 3),[11] or the use of a 2-(trimethylsilyl)ethanethiol derived component (eq 4),[12] permit high yields of unsymmetrical disulfides.





(4)

In systems having a tertiary amine and a sulfide unit, DMTSF demonstrates a chemoselectivity for sulfur (eq 5).[13]

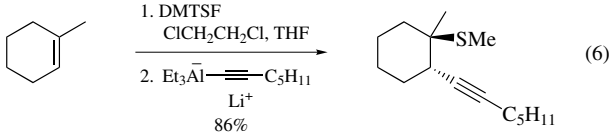


(5)

Allylic sulfides react with DMTSF chemoselectively at the sulfur atom, generating thiosulfonium ions. This ion formation is reversible and the allylic thiosulfonium ion is capable of a [2,3]-sigmatropic rearrangement before subsequent electrophilic addition to the alkene.[14]

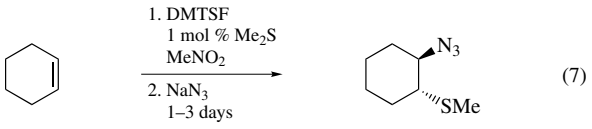
Methylsulfenylation of Alkenes. A key application of DMTSF in organic synthesis involves electrophilic addition to alkenes and subsequent addition of a nucleophile to the bridged sulfonium ion. Support for this mechanism is provided by the *anti* addition products observed.[15]

Carbon Nucleophiles. Most nucleophilic carbon sources are too basic for application to these reaction conditions. Alkynylalane ate complexes demonstrate an exception (eq 6).[16]

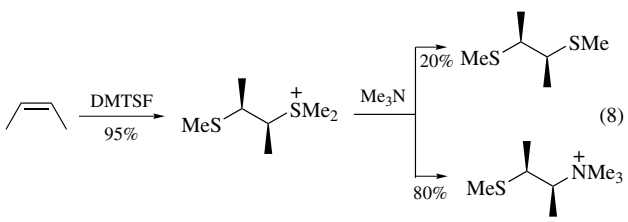


(6)

Nitrogen Nucleophiles. Nitrogen nucleophiles, specifically NH_3, amines, azide, and nitrite, resulted in high yields of alkene addition products (eq 7).[15a] In the absence of additional nucleophiles, the resulting sulfonium salt reacted with a tertiary amine to yield the demethylated product or the ammonium salt with a retention of configuration (eq 8).[15b]

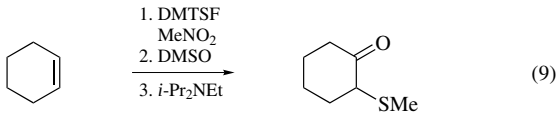


(7)



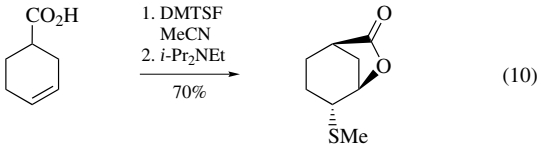
(8)

Oxygen Nucleophiles. Successful application of oxygen nucleophiles includes anhydrous KOAc (anti-Markovnikov product), $H_2O/CaCO_3$ (Markovnikov product), and DMSO which, upon treatment with diisopropylethylamine, yields α-methyl thioketones (eq 9).[17]



(9)

Electrophilic ring closure demonstrates another utility of DMTSF. Examples of sulfenyl etherification and sulfenyl lactonization have been reported (eq 10).[18]



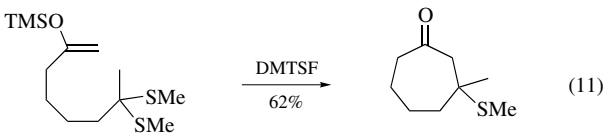
(10)

Phosphorus Nucleophiles. Triphenylphosphine is an effective nucleophile for reacting with the bridged sulfonium ion in high yield. The phosphonium salts generated eliminate MeSH upon reaction with base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, resulting in a synthesis of vinylphosphonium salts. If NaOH is used, a vinylphosphine oxide is generated.[19]

Other Nucleophiles. DMTSF and $Et_3N{\cdot}3HF$ react with alkenes to yield products formally of a MeSF addition. Yields are in excess of 80% and the reaction proceeds rapidly.[20] Homoallylic sulfides cyclized in the presence of DMTSF. The resulting sulfonium salt was successfully demethylated with Me_3N to yield 3-methylthiotetrahydrothiophenes.[21]

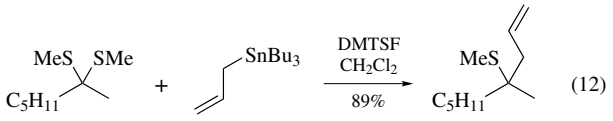
Dithioacetal, Trithioorthoester, and Thioglycoside Activation. DMTSF provides a chemoselective reagent for dithioacetal activation in the presence of electron-rich alkenes.[22] This bond-forming procedure complements the $TiCl_4$ mediated reaction between acetals and silyl enol ethers demonstrated by Mukaiyama. The generation of ketone precursors through dithioacetal carbanion (acyl anion equivalents) chemistry further amplifies the significance of DMTSF activation.

Dithioacetal Activation. DMTSF chemoselectively reacts with dithioacetals in the presence of a vinylsilane[22] and in the presence of a silyl enol ether (eq 11), resulting in cyclization.[23]



(11)

Many carbon nucleophiles tend to be too basic for successful addition to the carbocationic center provided by DMTSF activation of dithioacetals and usually result in vinyl sulfide formation. In addition, the Me_2S generated competes for the electrophilic center. Allylstannanes overcome these constraints and successfully generate new carbon–carbon bonds (eq 12).[24] DMTSF activation of a thioacetal resulted in an electrophilic cyclization at the 3-position of a 3-substituted indole.[25]



(12)

Trithioorthoester Activation. Electron-rich aromatic rings undergo electrophilic aromatic substitution with tris(phenylthio) methane in the presence of DMTSF. Subsequent hydrolysis results in an aldehyde and a net 'electrophilic formylation'.[6] Intramolecular reaction between a tris(phenylthio)methane unit and an alcohol represents an approach to lactone formation which utilizes the chemoselectivity of DMTSF.[26]

Thioglycoside Activation. A thioglycoside was successfully converted into a glycosyl fluoride with DMTSF.[7]

First Update

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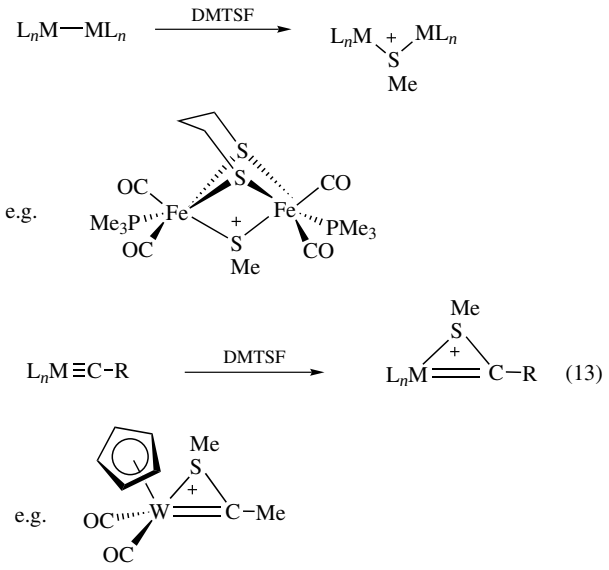
Methylsulfenylation of Nucleophilic Atoms.

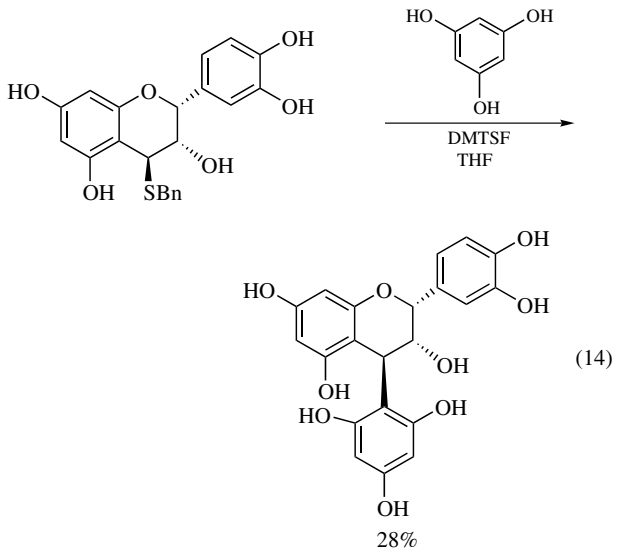
Methylsulfenylation of Metal Complexes. Metal complexes have been sulfenylated by the use of DMTSF. The methylsulfenyl group is either inserted into a metal-metal bond or added to a metal-carbon multiple bond (double or triple bond) (eq 13).[27,28]



(13)

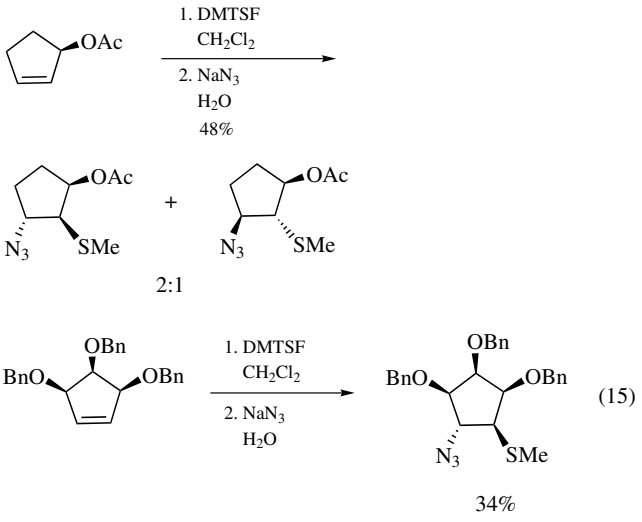
Methylsulfenylation of Sulfides. DMTSF can be used to remove several common thiol protecting groups to produce asymmetric methyl disulfides. Examples of such protecting groups are trimethylsilylethyl, trityl, benzyl, *p*-methoxybenzyl, and acetamidomethyl groups. If two protected thiol groups are present in the same molecule, disulfide bridge formation occurs.[29]

DMTSF reacts with flavan-3-ol-based benzyl sulfides with activation of the C_4–S bond towards substitution by carbon nucleophiles, allowing the formation of the interflavanyl bond in procyanidins (eq 14).[30]



(14)

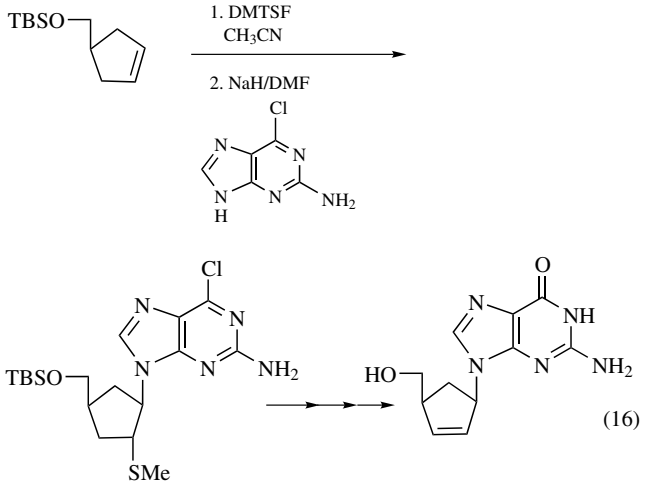
Methylsulfenylation of Alkenes. Azidosulfenylation of various substituted cyclopentenes with DMTSF in conjunction with azides[15] takes place in moderate yield with preferential methylsulfenylation, *syn* to the ring substituent(s) (eq 15).[31]

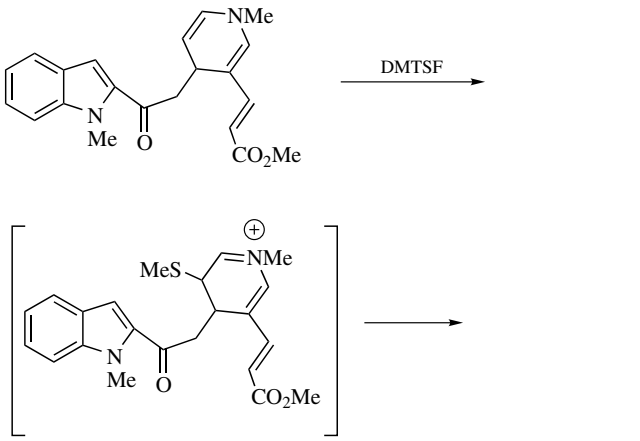


(15)

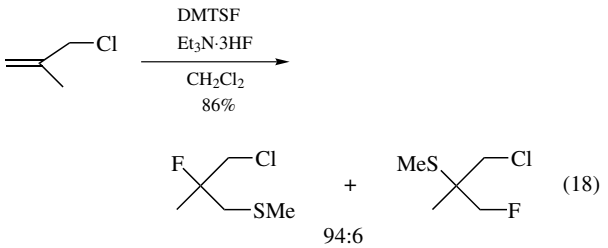
Cyclopentenes were also activated (with *anti*–directed methylsulfenylation) by DMTSF in the presence of nucleoside base anions yielding nucleoside analogs that could be converted into the antiviral agent Carbovir and related substances (eq 16).[32]

DMTSF-treatment of a dihydropyridine afforded an iminium ion, which was attacked intramolecularly by an indole moiety to form a key intermediate (albeit in a low yield) in a total synthesis of *N*-methylvitsine (eq 17).[33]

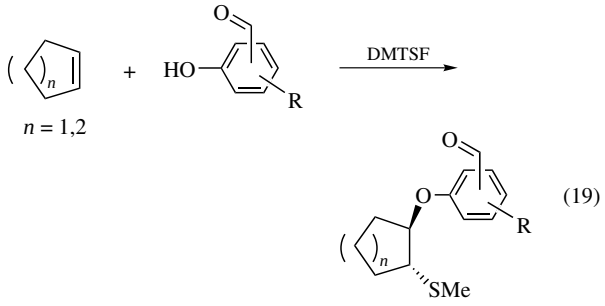




A further example of the use of DMTSF and $Et_3N{\cdot}3HF$[20] to produce Markovnikov-oriented fluoro methylthio ethers of methallyl chloride has been communicated (eq 18).[34]

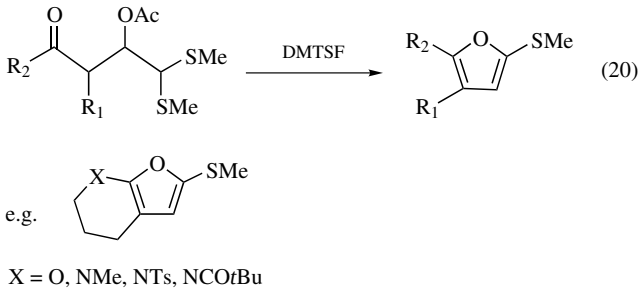


Addition of hydroxybenzaldehydes to DMTSF-activated cycloolefins were described as a first step in a library synthesis of methylsulfanylcycloalkoxyethers (eq 19).[35]

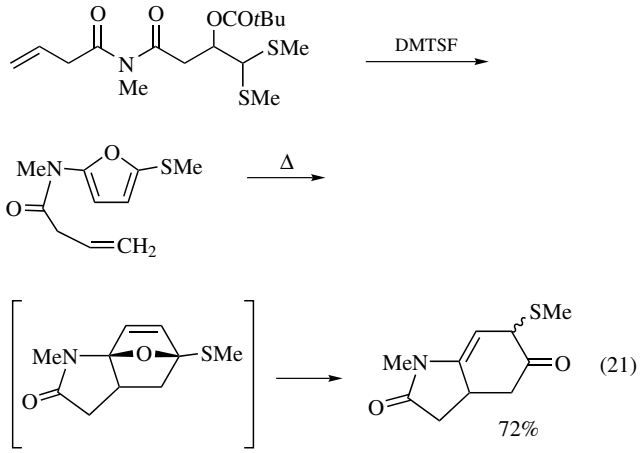


Activation of Thioacetals Including Thioglycosides.

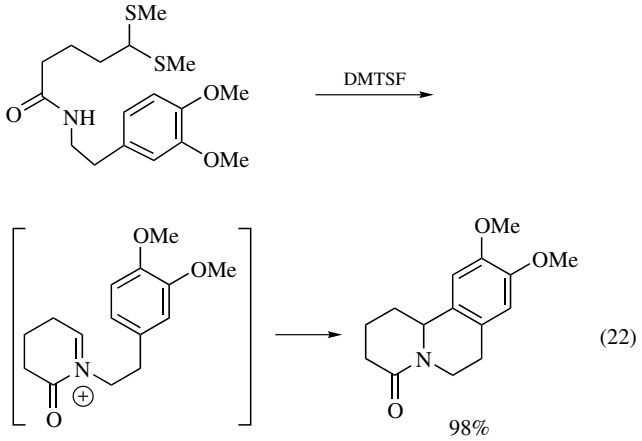
Dithioacetals. DMTSF-treatment of substituted 2-acyloxy-4-oxo-dithioacetals conveniently yields substituted 2-thiomethylfuran derivates in high yield (eq 20).[36] The reaction is rather substituent-independent and accepts both lactones, lactams, and carbamates, with the formation of bicyclic products.[37]



The presence of alkenes is also tolerated, which enables consecutive cycloaddition reactions leading to bi- or tricyclic targets (eq 21).[38]

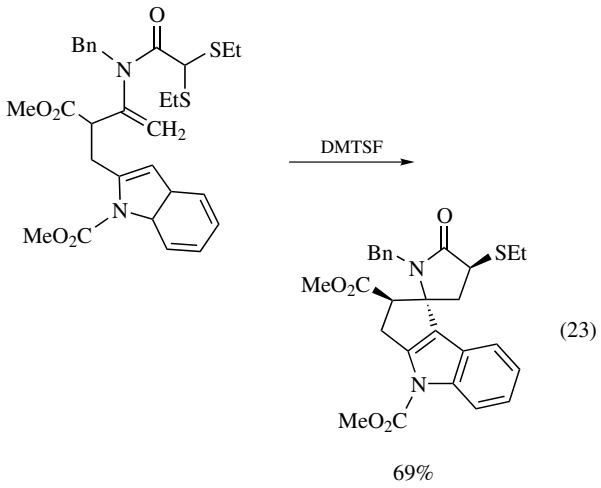


In systems bearing secondary amide based chains, the nitrogen atom may act as nucleophile resulting in Mannich-type intermediates. These can then be trapped by suitable electron rich aromatic rings to give azatricyclic ring systems (eq 22).[39]



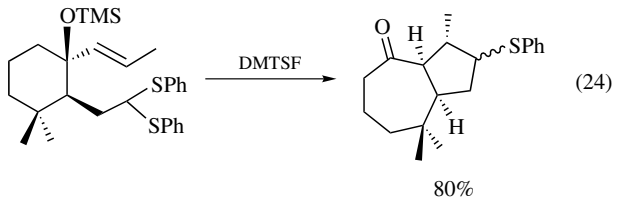
(22)

Alkenes can also be used as nucleophiles in this type of reaction (eq 23).[40]



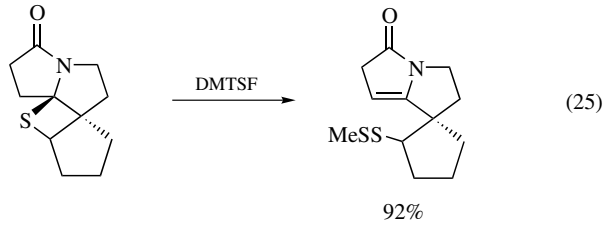
(23)

A further example of DMTSF activation of a dithioacetal followed by cyclization onto an olefin, this time with a subsequent pinacol rearrangement, was reported as part of a total synthesis of Shahamin K (eq 24).[41]



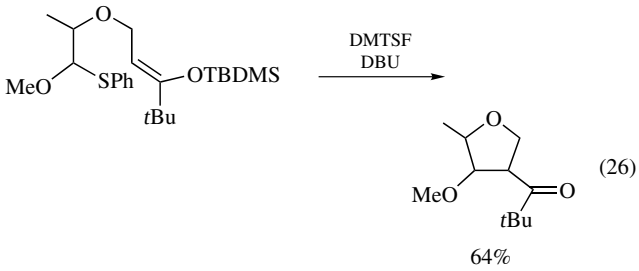
(24)

S,N-Acetals. Cyclic amidothietanes undergo ring opening to form asymmetric methyl disulfides when treated with DMTSF (eq 25).[42]



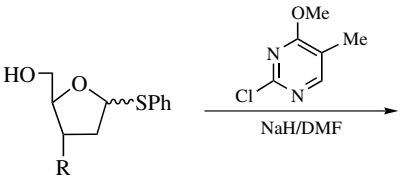
(25)

S,O-Acetals Including Thioglycosides. Activation of *S,O*-acetals with DMTSF in the presence of intramolecular silyl enol ethers affects cyclization (eq 26). As expected the activation is completely selective for the thiol group.[43]

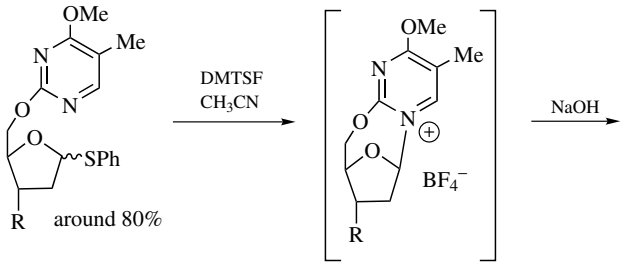


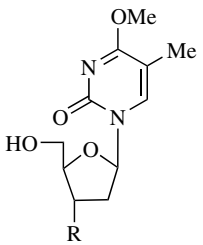
(26)

DMTSF has been used infrequently in the activation of thioglycosides with external acceptors,[7,44] for example, 2-deoxy donors[45] and in the release of solid phase-attached thioglycosides.[46] Usually the triflate salt, i.e. DMTST, is used, since normally the triflate is a better counterion in glycosylation reactions.[47] DMTSF has mainly been used in the context of synthesis of nucleosides and nucleotide analogs, using an internal glycosylation methodology. A pyrimidine base was attached to a hydroxyl group (most often 5-OH of a ribose derivative) via alkylation. Activation of the thioglycoside by DMTSF was followed by an intramolecular attack of a pyrimidine ring nitrogen to afford a bicyclic *N*-glycoside pyridinium intermediate, which was hydrolyzed with base to yield the desired nucleoside (eq 27).[48] Opening of the intermediate with different sulfur and nitrogen



R= H, F or N_3



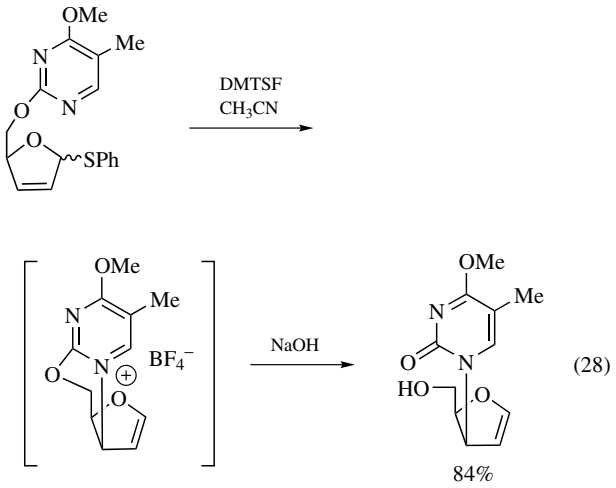


(27)

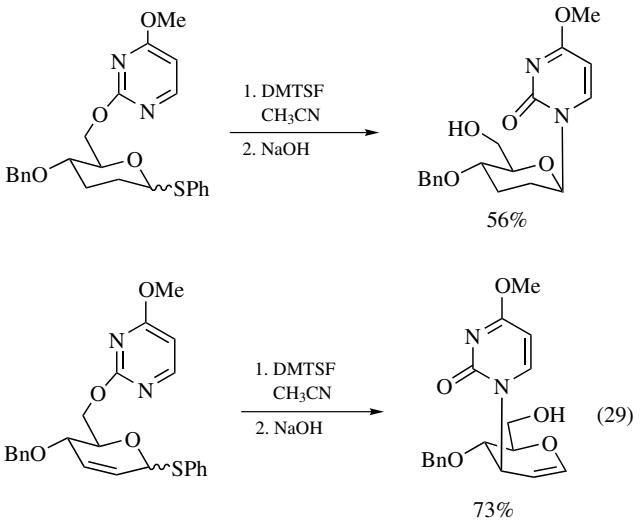
R = H 79%
R = F 84%
R = N_3 86%

nucleophiles afforded 5′-substituted analogs.[49] Many variants of both the precursor thioglycoside and pyrimidine base have been used to produce different target analogs.[50]

When a 2′,3′-unsaturated pentafuranose thioglycoside is utilized allylic displacement is observed and the product is the 3′-isomeric nucleoside (eq 28).[51]

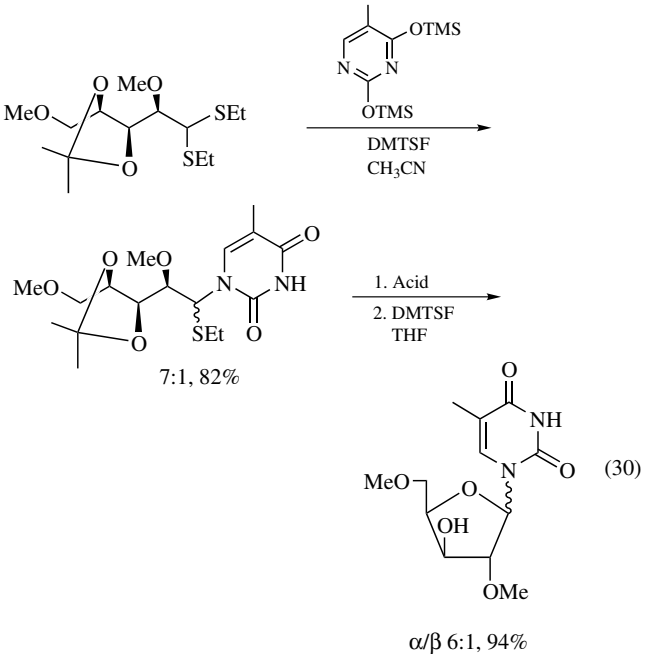


Similar processes, both direct and allylic nucleophilic displacements, are observed when hexopyranose thioglycosides bearing a pyrimidine ring on the 6-OH group are activated with DMTS (eq 29).[52]



Nucleosides have also been synthesized starting from open-chain dithioacetals in a three-step procedure involving introduction of the base, deprotection, and cyclization. In the first (dithioacetal) and last step (*N*,*S*-acetal) DMTSF was used as reagent (eq 30).[53]

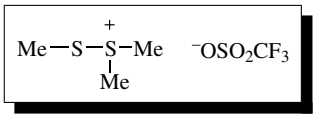
Related Reagents. Dimethyl(methylthio)sulfonium Trifluoromethanesulfonate (DMTST); *N*-Iodosuccinimide; *N*-Iodosaccharin; 1-Benzenesulfinyl Piperidine; Diphenyl Sulfoxide.



1. (a) Meerwein, H.; Zenner, K.-F.; Gipp, R., *Justus Liebigs Ann. Chem.* 1965, *688*, 67. (b) Alternate reagent: dimethyl(thiomethyl)sulfonium 2,4,6-trinitrobenzenesulfonate: Helmkamp, G. K.; Cassey, H. N.; Olsen, B. A.; Pettitt, D. J., *J. Org. Chem.* **1965**, *30*, 933. (c) Review: Horito, S.; Hashimoto, H., *Yuki Gosei Kagaku Kyokai Shi* **1990**, *48*, 1028 (*Chem. Abstr.* **1991**, *114*, 121 385k).
2. Minato, H.; Miura, T.; Kobayashi, M., *Chem. Lett.* **1975**, 701.
3. Trost, B. M.; Shibata, T.; Martin, S. J., *J. Am. Chem. Soc.* **1982**, *104*, 3228.
4. (a) Kline, M. L.; Beutow, N.; Kim, J. K.; Caserio, M. C., *J. Org. Chem.* **1979**, *44*, 1904. (b) O'Malley, G. J.; Cava, M. P., *Tetrahedron Lett.* **1985**, *26*, 6159.
5. Trost, B. M.; Murayama, E., *J. Am. Chem. Soc.* **1981**, *103*, 6529.
6. Smith, R. A. J.; Bin Manas, A. R., *Synthesis* **1984**, 166.
7. Blomberg, L.; Norberg, T., *J. Carbohydr. Chem.* **1992**, *11*, 751.
8. Meerwein, H.; Zenner, K.-F.; Gipp, R., *Justus Liebigs Ann. Chem.* **1965**, *688*, 67.
9. Minato, H.; Miura, T.; Kobayashi, M., *Chem. Lett.* **1975**, 701.
10. (a) Lawesson's Reagent: Zabirov, N. G.; Cherkasov, R. A.; Khalikov, I. S.; Pudovik, A. N., *Zh. Obshch. Khim.* **1986**, *56*, 2673 (*Chem. Abstr.* **1987**, *107*, 236 846j) . (b) Sulfur: Bruzik, K. S.; Salamonczyk, G.; Stec, W. J., *J. Org. Chem.* **1986**, *51*, 2368. (c) Dibenzoyl disulfide: Schönberg reaction: Kamer, P. C. J.; Roelenm, H. C. P. F.; van den Elst, G. A.; van der Marel, G. A.; van Boom, J. H., *Tetrahedron Lett.* **1989**, *30*, 6757. (d) Tetraethylthiuram disulfide: Vu, H.; Hirschbein, B. L., *Tetrahedron Lett.* **1991**, *32*, 3005. (e) 3*H*-1, 2-Benzodithiole-3-one 1, 1-dioxide: Iyer, R. P.; Egan, W.; Regan, J. B.; Beaucage, S. L., *J. Am. Chem. Soc.* **1990**, *112*, 1253.
11. Dubs, P.; Stüssi, R., *Helv. Chim. Acta* **1976**, *59*, 1307.
12. Anderson, M. B.; Ranasinghe, M. G.; Palmer, J. T.; Fuchs, P. L., *J. Org. Chem.* **1988**, *53*, 3125.
13. Kim, J. K.; Souma, Y.; Beutow, N.; Ibbeson, C.; Caserio, M. C., *J. Org. Chem.* **1989**, *54*, 1714.
14. Kim, J. K.; Caserio, M. C., *Tetrahedron Lett.* **1981**, *22*, 4159.
15. (a) Trost, B. M.; Shibata, T., *J. Am. Chem. Soc.* **1982**, *104*, 3225. (b) Caserio, M. C.; Kim, J. K., *J. Am. Chem. Soc.* **1982**, *104*, 3231.
16. Trost, B. M.; Martin, S. F., *J. Am. Chem. Soc.* **1984**, *106*, 4263.
17. Trost, B. M.; Shibata, T.; Martin, S. J., *J. Am. Chem. Soc.* **1982**, *104*, 3228.
18. O'Malley, G. J.; Cava, M. P., *Tetrahedron Lett.* **1985**, *26*, 6159.

19. (a) Okuma, K.; Koike, T.; Yamamoto, S.-i.; Yonekura, K.; Ohta, H., *Chem. Lett.* **1989**, 1953. (b) Okuma, K.; Koike, T.; Yamamoto, S.-i.; Takeuchi, H.; Yonekura, K.; Ono, M.; Ohta, H., *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2375.
20. (a) Haufe, G.; Alvernhe, G.; Anker, D.; Laurent, A.; Saluzzo, C., *Tetrahedron Lett.* **1988**, *29*, 2311. (b) Haufe, G.; Alvernhe, G.; Anker, D.; Laurent, A.; Saluzzo, C., *J. Org. Chem.* **1992**, *57*, 714.
21. Kline, M. L.; Beutow, N.; Kim, J. K.; Caserio, M. C., *J. Org. Chem.* **1979**, *44*, 1904.
22. Trost, B. M.; Murayama, E., *J. Am. Chem. Soc.* **1981**, *103*, 6529.
23. Braish, T. F.; Saddler, J. C.; Fuchs, P. L., *J. Org. Chem.* **1988**, *53*, 3647.
24. Trost, B. M.; Sato, T., *J. Am. Chem. Soc.* **1985**, *107*, 719.
25. Amat, M.; Alvarez, M.; Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Lavilla, R.; Gracía, X.; Bosch, J., *Tetrahedron Lett.* **1990**, *31*, 3453.
26. Posner, G. H.; Asirvatham, E.; Hamill, T. G.; Webb, K. S., *J. Org. Chem.* **1990**, *55*, 2132.
27. Kreissl, F. R.; Schuett, W.; Stegmair, C. M.; Ullrich, N.; Keller, H.; Ostermeier, J.; Herdtweck, E., *Chem Ber.* **1993**, *126*, 1609.
28. Georgakaki, I. P.; Miller, M. L.; Darensbourg, M. Y., *Inorg. Chem.* **2003**, *42*, 2489.
29. Bishop, P.; Jones, C.; Chmielewski, J., *Tetrahedron Lett.* **1993**, *34*, 4469.
30. Steynberg, P. J.; Nel, R. J. J.; Van Rensburg, H.; Bezuidenhoudt, B. C. B.; Ferreira, D., *Tetrahedron* **1998**, *54*, 8153.
31. Clark, M. A.; Goering, B. K.; Li, J.; Ganem, B., *J. Org. Chem.* **2000**, *65*, 4058.
32. Jung, M. E.; Rhee, H., *Tetrahedron Lett.* **1993**, *34*, 4449.
33. Bennasar, M. L.; Vidal, B.; Bosch, J., *Chem. Commun.* **1995**, 125.
34. Haufe, G.; Wessel, U.; Schulze, K.; Alvernhe, G., *J. Fluorine Chem.* **1995**, *74*, 283.
35. Krueger, C. A.; Chiu, B. C.; Walters, M. A. Abstracts of Papers, *224th ACS National Meeting* **2002**, ORGN-151.
36. Padwa, A.; Ginn, J. D.; McClure, M. S., *Org. Lett.* **1999**, *1*, 1559.
37. Padwa, A.; Eidell, C. K.; Ginn, J. D.; McClure, M. S., *J. Org. Chem.* **2002**, *67*, 1595.
38. (a) Ginn, J. D.; Lynch, S. M.; Padwa, A., *Tetrahedron Lett.* **2000**, *41*, 9387. (b) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M., *J. Org. Chem.* **2002**, *67*, 3412. (c) Padwa, A.; Eidell, C. K.; Lynch, S. M., *Heterocycles* **2002**, *58*, 227.
39. (a) Padwa, A.; Waterson, A. G., *Tetrahedron Lett.* **1998**, *39*, 8585. (b) Padwa, A.; Waterson, A. G., *J. Org. Chem.* **2000**, *65*, 235.
40. Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S.; Wang, Q., *J. Org. Chem.* **2002**, *67*, 5928.
41. Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J., *J. Am. Chem. Soc.* **2001**, *123*, 4851.
42. (a) Padwa, A.; Jacquez, M. N.; Schmidt, A., *Org. Lett.* **2001**, *3*, 1781. (b) Padwa, A.; Jacquez, M. N.; Schmidt, A., *J. Org. Chem.* **2004**, *69*, 33.
43. Craig, D.; King, N. P.; Shaw, A. N., *Tetrahedron Lett.* **1997**, *38*, 8599.
44. Aaberg, P. M. l.; Blomberg, L.; Loenn, H.; Norberg, T., *J. Carbohydr. Chem.* **1994**, *13*, 141.
45. Lear, M. J.; Yoshimura, F.; Hirama, M., *Angew. Chem., Int. Ed.* **2001**, *40*, 946.
46. Rademann, J.; Schmidt, R. R., *Tetrahedron Lett.* **1996**, *37*, 3989.
47. Garegg, P. J., *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.
48. (a) Sujino, K.; Sugimura, H., *Tetrahedron Lett.* **1994**, *35*, 1883. (b) Sujino, K.; Sugimura, H., *Chem. Lett.* **1993**, 1187.
49. Sugimura, H.; Katoh, Y., *Chem. Lett.* **1999**, 361.
50. (a) Sugimura, H.; Motegi, M.; Sujino, K., *Nucleosides & Nucleotides* **1995**, *14*, 413. (b) Yokomatsu, T.; Shimizu, T.; Sada, T.; Shibuya, S., *Heterocycles* **1999**, *50*, 21. (c) Sugimura, H.; Sujino, K., *Yuki Gosei Kagaku Kyokaishi* **2001**, *59*, 879.
51. Sujino, K.; Sugimura, H., *Chem. Commun.* **1994**, 2541.
52. (a) Sugimura, H., *Nucleosides, Nucleotides & Nucleic Acids* **2000**, *19*, 629. (b) Sugimura, H., *Nucleic Acid Res. Suppl.* **2003**, 21.
53. Guindon, Y.; Gagnon, M.; Thumin, I.; Chapdelaine, D.; Jung, G.; Guerin, B., *Org. Lett.* **2002**, *4*, 241.

Dimethyl(methylthio)sulfonium Trifluoromethanesulfonate



[85055-60-3] $C_3H_9S_2^+ CF_3O_3S^-$ (MW 258.30)

InChI = 1/C3H9S2.CHF3O3S/c1-4-5(2)3;2-1(3,4)8(5,6)7/h1-3H3;(H,5,6,7)/q+1;/p-1/fC3H9S2.CF3O3S/qm;-1

InChIKey = TXVLFCLSVCYBIV-VEHBGLORCV

(methylsulfenylating agent; activates thioglycosides and other types of glycosyl donors for glycoside synthesis[1–3])

Alternate Name: dimethyl(methylthio)sulfonium triflate, dimethylthiomethyl sulfonium trifluoromethanesulfonate, DMTST.

Physical Data: mp 28–36 °C;[4] 53–55 °C.[5] Variation in reported melting points is probably due to the hygroscopic nature of the reagent.

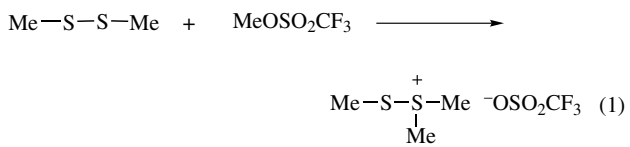
Solubility: soluble in CH_2Cl_2, MeCN, $MeNO_2$; sparingly soluble in diethyl ether, benzene, toluene; insoluble in petroleum ether.

Form Supplied in: white crystals; not commercially available.

Analysis of Reagent Purity: ^{1}H NMR.

Purification: recrystallization from dichloromethane–diethyl ether.

Preparative Methods: readily prepared by alkylation of methyl disulfide with methyl trifluoromethanesulfonate in dichloromethane[1,4,5] or neat[6] (eq 1). The reagent crystallizes from dichloromethane by the addition of diethyl ether. Alternatively, the dichloromethane solution can be used directly for most applications.



(1)

Handling, Storage, and Precautions: the reagent is hygroscopic, it liquifies in air. Store in a closed vessel or over a strong drying agent, preferably, in the refrigerator. A 1 M solution in dichloromethane, which partially crystallizes on storage in the refrigerator, can be stored for prolonged periods of time.[1] In cases of doubts the use of freshly prepared DMTST is recommended.

Original Commentary

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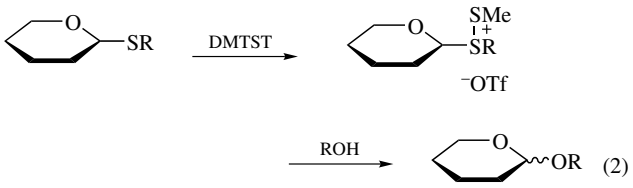
Introduction. The sulfur–sulfur bond in alkylated disulfides [dialkyl(alkylthio)sulfonium salts] is susceptible to nucleophiles and thus alkylated disulfides are alkylsulfenylating agents, or

potential sources of alkylsulfenyl (RS^+) ions.[7,8] This, in combination with the excellent leaving property of the triflate group, led to the introduction of dimethyl(methylthio)sulfonium triflate (DMTST) as a synthetic reagent for activation of thioglycosides in glycosylation reactions,[1–3] which is still its primary use. Other applications of the reagent (acetalization, addition to unsaturated compounds) are also based on its alkylsulfenylating capability.

Glycosylation.

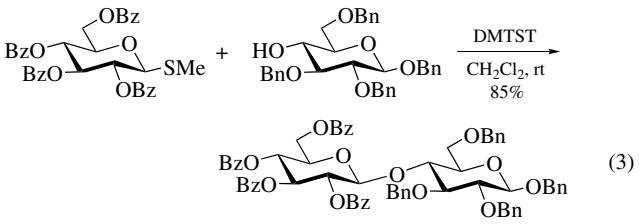
Syntheses of O-Glycosides from Thioglycosides. Thioglycosides have the advantage over most glycosylating agents that they are stable, are easy to functionalize, can serve both as glycosyl acceptors and glycosyl donors, and are therefore widely used in oligosaccharide syntheses.[9,10] DMTST, a highly thiophilic reagent, activates thioglycosides for glycosylations. It has been used in a large number of oligosaccharide syntheses for the construction of diverse glycosidic and interglycosidic linkages.

Activation of thioglycosides by DMTST takes place by sulfenylation of the thioglycoside sulfur. The resulting positively charged intermediate then can react directly or, more probably, through the common intermediates of glycosylation reactions (oxocarbonium ions, acyloxonium ions, glycosyl triflates) with alcohols (or other nucleophiles) to give glycosides (eq 2).



(2)

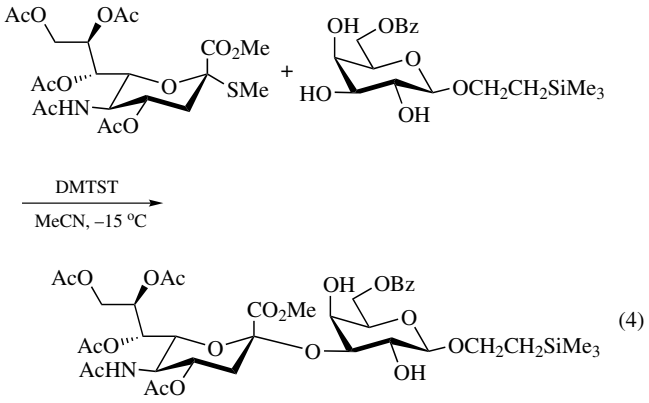
In the presence of neighboring group participating substituents the glycosylations lead to 1,2-*trans*-glycosides, as shown in the synthesis of the cellobioside derivative (eq 3).[1]



(3)

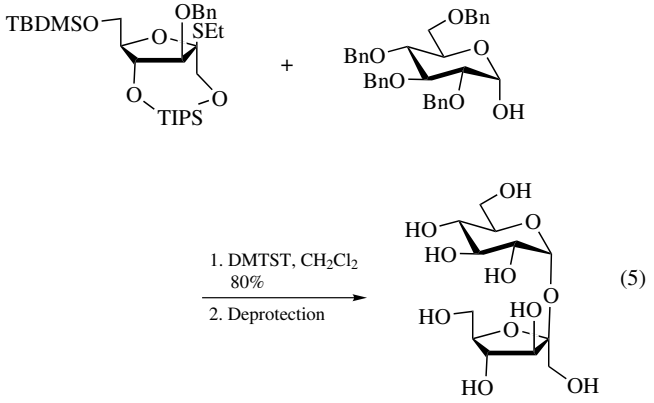
Reactions are usually performed at or below room temperature in solvents such as dichloromethane or acetonitrile with a 3–5-fold excess of the reagent. The reaction mixture may be buffered with 2,6-di-*tert*-butyl-4-methylpyridine or other sterically hindered bases if required. DMTST has been used to activate a variety of different monosaccharides including thioglycoside derivatives of D-glucose,[1,2,11] D-galactose,[1,12–14] D-mannose,[15] D-fructofuranose,[16] amino sugars,[1,12,17] uronic acids[15,18] and heptoses.[19] Di-,[13,14,17] tri-,[20,21] tetra-,[22] and even pentasaccharide[23] thioglycosides have also been activated by this reagent. The most frequently used neighboring group participating protecting groups are *O*-acetyl, *O*-pivaloyl and *O*-benzoyl; for amino functions *N*-phthaloyl[1,12,17] and *N*-trichloroethoxycarbonyl[24,25] are the most frequently used ones. Reactions with *O*-benzoyl-protected thioglycosides tend to give higher yields and cleaner reactions than those of *O*-acetyl protected ones.[1,18] The thioglycosides commonly used in conjunction with DMTST have simple thioalkyl (SMe, SEt) and thioaryl (SPh, STol) groups; heterocyclic thioglycosides have been used occasionally.[26] A wide range of alcohols, including mono- and oligosaccharides, as well as peptides,[24,25,27] has been used as glycosyl acceptors. It should be noted that although neighboring group participation is generally used to govern the formation of *trans*-glycosides, several examples of stereoselective synthesis of *trans*-glycosides without neighboring group participation in DMTST-promoted glycosylations are also known.[19,28,29]

DMTST-promoted glycosylations with thioglycosides having non-participating substituents result in anomeric mixtures of *O*-glycosides,[2] but very often useful, or even complete, stereoselectivity can be achieved. Methods increasing the stereoselectivity include the addition of bromide ion to the glycosylation mixture,[2] changing the solvent,[2] tuning the reactivity of the glycosyl donors and acceptors by the proper choice of the protecting groups, and intramolecular aglycon delivery. Addition of *tetra*-butylammonium bromide to the glycosylation mixture results in the in situ formation of a glycosyl bromide, which then reacts in a halide ion-catalyzed glycosylation reaction[30] to yield 1,2-*cis*-glycosides. Performing the reaction in acetonitrile at low temperature changes the stereoselectivity due to the formation of nitrilium ion intermediates.[2] Application of this principle to the biologically important sugar *N*-acetylneuraminic acid, resulted in a very useful synthesis of α-glycosides of *N*-acetylneuraminic acid[31,32] (eq 4), previously accessible only with great difficulty.

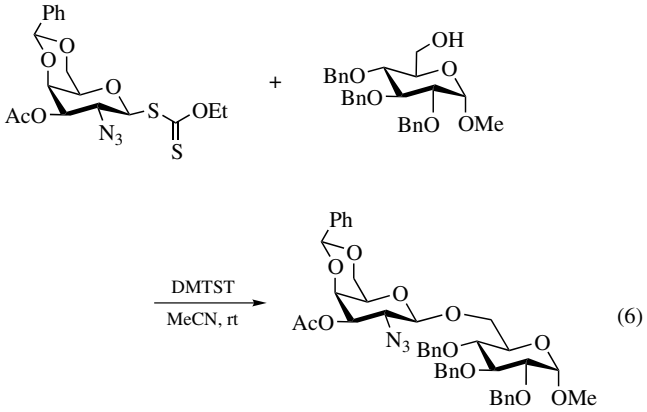


(4)

Ethereal solvents and solvents of low polarity such as benzene also shift the stereoselectivity towards *cis*-glycosides. Although DMTST is poorly soluble in diethyl ether or benzene, its solubility is sufficient for reactions to proceed.[33] A large number of stereoselective α-L-fucosylations have been performed this way, as for example in the total synthesis of the biologically important sialyl Lewis x oligosaccharide.[14] Internal aglycon delivery, i.e. performing the glycosylation on a tethered derivative of the glycosyl donor and acceptor, was found to be a valuable tool for the synthesis of β-D-fructofuranosides.[34,35] Whereas common glycosylations with D-fructofuranosyl donors give a preponderance of α-D-fructoside,[16] reactions of tethered derivatives gave exclusively the β-D-fructofuranosides. In an analogous manner DMTST-promoted reaction of the intramolecularly locked fructofuranosyl donor in eq 5 resulted in the first stereoselective, high-yielding synthesis of sucrose[36] (eq 5).



(5)



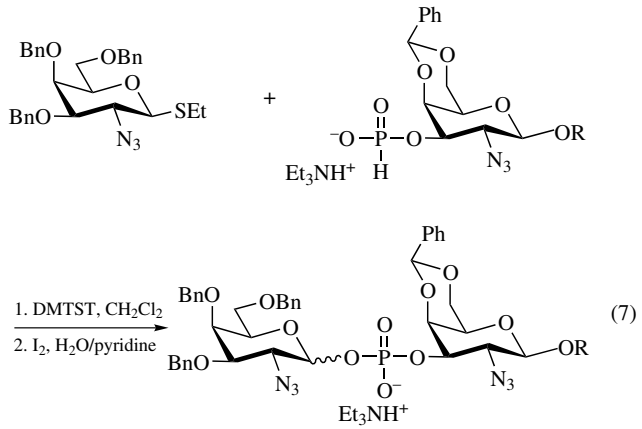
(6)

Compared with other promoters (methyl trifluoromethanesulfonate and the *N*-iodosuccinimide trifluoromethanesulfonic acid [NIS-TfOH] system) frequently used in glycosylation reactions with thioglycoside donors, DMTST is more efficient[3,27] than methyl triflate, but it is less powerful than NIS–TfOH. DMTST has the advantage that side-reactions, such as alkylation of the acceptor (which can be encountered in methyl triflate-promoted reactions[1,37]), formation of glycosyl-succinimides,[16,38,39] or iodination of certain protecting groups[40] can be avoided. The related compound, dimethyl(methylthio)sulfonium tetrafluoroborate, which was introduced as a glycosylation promoter at the same time as DMTST,[1] also found application in oligosaccharide synthesis.[41] However, DMTSF-promoted glycosylations are likely to proceed through glycosyl fluoride intermediates, as glycosyl fluorides have been isolated in reactions of thioglycosides with the fluoroborate salt performed in the absence of glycosyl acceptors.[42]

The reactivity differences of thioglycosides depending on their substituents in the carbohydrate unit ('armed-disarmed' donors[43,44]) or in the thioaglycon ('latent-active' donors[45–47]) permit the use of thioglycosides both as glycosyl donors and glycosyl acceptors in the same reaction. Glycosylation of an unreactive thioglycoside with a more reactive one takes place without self-condensation of the acceptor. This was elegantly exploited in the programmable one-pot oligosaccharide synthesis developed by Wong.[38,39] DMTST has found application in one-pot oligosaccharide synthesis, where its use is especially beneficial when the reactivities of glycosyl donors are relatively high.[38,39] Chain termination by the accumulation of glycosylsuccinimide byproducts formed in NIS-promoted reactions is avoided in DMTST-promoted reactions. Among the applications of DMTST in oligosaccharide synthesis, its use in the solid-phase synthesis of large and structurally complex oligosaccharides[11,21,48] and in the combinatorial synthesis of oligosaccharide libraries[6,38,39] deserves particular attention.

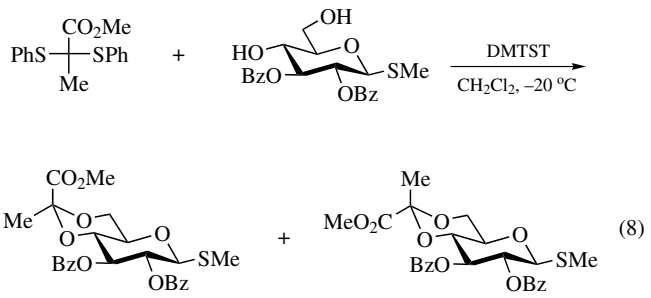
Syntheses of O-Glycosides from Compounds Other than Thioglycosides. Other types of compounds having a thio functionality at the anomeric center can be activated by DMTST. Anomeric *S*-xanthates[49,50] (eq 6) and dithiocarbamates[51] have also been used as glycosyl donors in combination with the reagent. Isopropenyl glycosides,[52] though not having sulfur at the anomeric leaving group, could also be activated for glycoside synthesis with DMTST.

Syntheses of Other Types of Compounds from Thioglycosides. DMTST promotes the reaction of thioglycosides with nucleophiles other than alcohols. Glycosylation of *H*-phosphonate monoesters followed by oxidation of the phosphonate diester was found to be a viable alternative to glycosyl phosphodiesters not accessible by other methods (eq 7).[53] Reaction of thioglycosides with pyrimidine bases gave nucleoside analogs,[54–56] reaction with water constitutes a mild hydrolysis of thioglycosides to the hemiacetal[57] and reaction with alcohols in the presence of excess base was used for the synthesis of orthoesters.[58] The formation of glycosyl bromides from thioglycosides with the aid of DMTST and bromide ions[2] was discussed earlier.



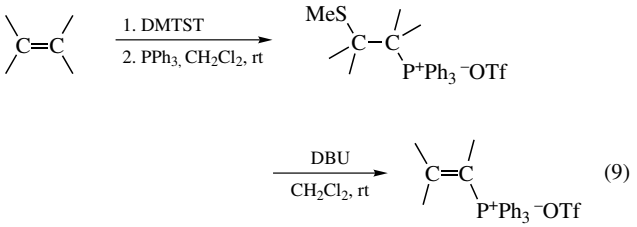
(7)

Acetalization. Cyclic acetals of pyruvic acid are not easily prepared by using commonly available acetalization methods. Cyclic pyruvic acid acetals of carbohydrates were prepared by DMTST-promoted transacetalization reaction between methyl pyruvate diphenyl dithioacetal and carbohydrate diols (eq 8).[59]



(8)

Addition to Double Bonds. Compared with other alkylsulfenylating agents, addition of dimethyl(methylthio)sulfonium trifluoromethanesulfonate to double bonds is less frequently used. Treatment of olefins with the reagent followed by the addition of triphenylphosphine gave 2-methylthioalkylphosphonium salts in high yields, which could be converted into vinylphosphonium salts or vinyl phosphine oxides (eq 9).[5]



(9)

Addition of the reagent to double bonds[60,61] limits the use of unsaturated protecting groups (e.g. allyl, allyloxycarbonyl) in dimethyl(methylthio)sulfonium triflate-promoted glycosylation reactions.

First Update

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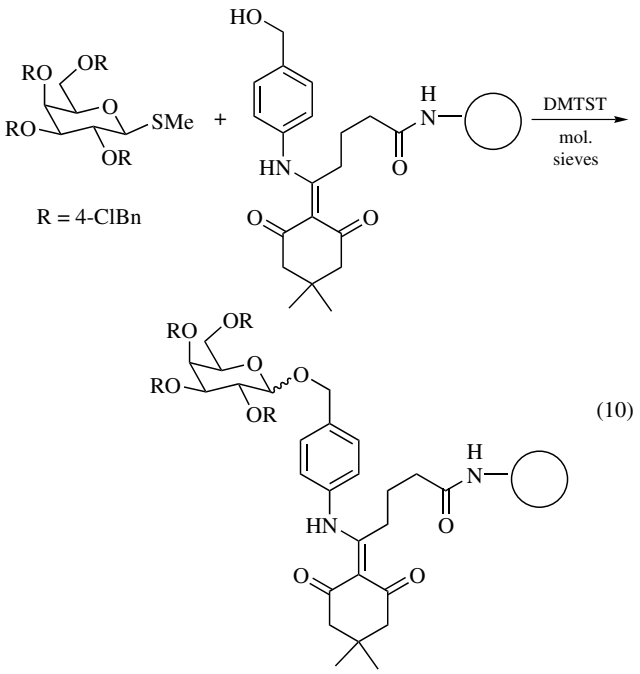
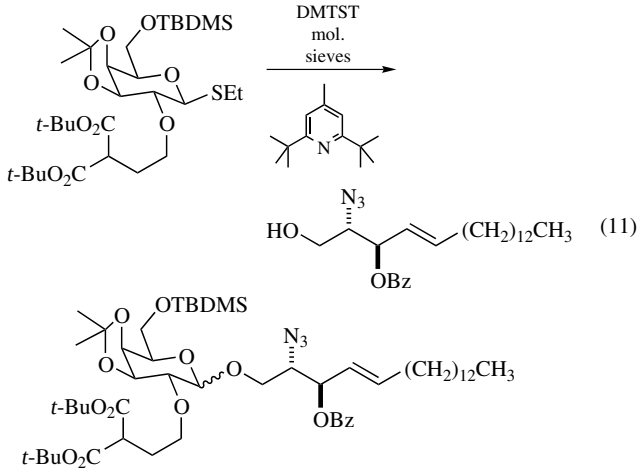
Glycosylation. The use of DMTST continues to be an important way to activate thioglycosides for the synthesis of polysaccharides and other *O*-glycosides (e.g., eq 2),[62] including the immobilizing of monosaccharide donors in solid-phase synthesis of oligosaccharides (eq 10).[63]



(10)

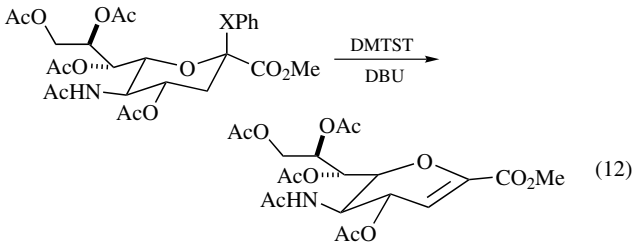
The α/β anomer ratio of *O*-glycoside products obtained in reactions promoted by DMTST was reported to be different than the ratio obtained using DMTSF,[64] supporting the hypothesis that the mechanisms for reactions involving these two reagents are distinct.

For thioglycosides with low donor activity, DMTST is less effective than promotion of the glycosylation reaction with the NIS/AgOTf system.[65] DMTST is useful for the reaction of thioglycosides with acceptors containing unsaturation (eq 11).[66] In some cases, acid-sensitive protecting groups (e.g., silyl ethers) may transfer or be cleaved under reaction conditions that include DMTST.[66,67]



(11)

Eliminations. Exposure of α-phenylsulfanyl and α-phenylselenyl derivatives of neuraminic acid to DMTST and DBU effected an elimination reaction to give unsaturated compounds (eq 12).[68] Interestingly, no reaction occurred with methylsulfanyl derivatives under the same conditions.



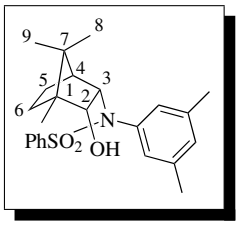
(12)

Related Reagents. Dimethyl(methylthio)sulfonium Fluoroborate (DMTSF); Dimethyl(methylthio)sulfonium Tetrafluoroborate, Methylsulfenyl Trifluoromethanesulfonate, Methyl Trifluoromethanesulfonate, *N*-Iodosuccinimide (with Triflic Acid).

1. Fügedi, P.; Garegg, P. J., *Carbohydr. Res.* **1986**, *149*, C9.
2. Andersson, F.; Fügedi, P.; Garegg, P. J.; Nashed, M., *Tetrahedron Lett.* **1986**, *27*, 3919.
3. Andersson, F.; Birberg, W.; Fügedi, P.; Garegg, P. J.; Nashed, M.; Pilotti, Å., *ACS Symp. Ser.* **1989**, *386*, 117.
4. Ravenscroft, M.; Roberts, R. M. G.; Tillett, J. G., *J. Chem. Soc., Perkin Trans. 2* **1982**, 1569.
5. Okuma, K.; Koike, T.; Yamamoto, S.; Takeuchi, H.; Yonekura, K.; Ono, M.; Ohta, H., *Bull. Chem. Soc. Japan* **1992**, *65*, 2375.

6. Wong, C. H.; Ye, X. S.; Zhang, Z. Y., *J. Am. Chem. Soc.* **1998**, *120*, 7137.
7. Helmkamp, G. K.; Olsen, B. A.; Pettitt, D. J., *J. Org. Chem.* **1965**, *30*, 676.
8. Smallcombe, S. H.; Caserio, M. C., *J. Am. Chem. Soc.* **1971**, *93*, 5826.
9. Fügedi, P.; Garegg, P. J.; Lönn, H.; Norberg, T., *Glycoconjugate J.* **1987**, *4*, 97.
10. Garegg, P. J., *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.
11. Nicolaou, K. C.; Winssinger, N.; Pastor, J.; DeRoose, F., *J. Am. Chem. Soc.* **1997**, *119*, 449.
12. Kiso, M.; Katagiri, H.; Furui, H.; Hasegawa, A., *J. Carbohydr. Chem.* **1992**, *11*, 627.
13. Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A., *Carbohydr. Res.* **1990**, *200*, 269.
14. Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A., *Carbohydr. Res.* **1991**, *209*, C1.
15. Garegg, P. J.; Olsson, L.; Oscarson, S., *Bioorg. Med. Chem.* **1996**, *4*, 1867.
16. Krog-Jensen, C.; Oscarson, S., *J. Org. Chem.* **1996**, *61*, 1234.
17. Nilsson, M.; Norberg, T., *Carbohydr. Res.* **1988**, *183*, 71.
18. Garegg, P. J.; Olsson, L.; Oscarson, S., *J. Org. Chem.* **1995**, *60*, 2200.
19. Ekelöf, K.; Oscarson, S., *J. Carbohydr. Chem.* **1995**, *14*, 299.
20. Ishida, H. K.; Ishida, H.; Kiso, M.; Hasegawa, A., *Tetrahedron: Asymmetry* **1994**, *5*, 2493.
21. Nicolaou, K. C.; Watanabe, N.; Li, J.; Pastor, J.; Winssinger, N., *Angew. Chem., Int. Ed.* **1998**, *37*, 1559.
22. Chernyak, A.; Oscarson, S.; Turek, D., *Carbohydr. Res.* **2000**, *329*, 309.
23. Ruda, K.; Lindberg, J.; Garegg, P. J.; Oscarson, S.; Konradsson, P., *J. Am. Chem. Soc.* **2000**, *122*, 11067.
24. Schultz, M.; Kunz, H., *Tetrahedron Lett.* **1992**, *33*, 5319.
25. Schultz, M.; Kunz, H., *Tetrahedron: Asymmetry* **1993**, *4*, 1205.
26. Takeda, K.; Tsuboyama, K.; Torii, K.; Furuhata, K.; Sato, N.; Ogura, H., *Carbohydr. Res.* **1990**, *203*, 57.
27. Paulsen, H.; Rauwald, W.; Weichert, U., *Liebigs Ann. Chem.* **1988**, 75.
28. Hällgren, C.; Hindsgaul, O., *Carbohydr. Res.* **1994**, *260*, 63.
29. Bernlind, C.; Oscarson, S., *Carbohydr. Res.* **1997**, *297*, 251.
30. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K., *J. Am. Chem. Soc.* **1975**, *97*, 4056.
31. Murase, T.; Ishida, H.; Kiso, M.; Hasegawa, A., *Carbohydr. Res.* **1988**, *184*, C1.
32. Kanie, O.; Kiso, M.; Hasegawa, A., *J. Carbohydr. Chem.* **1988**, *7*, 501.
33. Garegg, P. J.; Oscarson, S.; Ritzén, H.; Szönyi, M., *Carbohydr. Res.* **1992**, *228*, 121.
34. Krog-Jensen, C.; Oscarson, S., *J. Org. Chem.* **1996**, *61*, 4512.
35. Krog-Jensen, C.; Oscarson, S., *J. Org. Chem.* **1998**, *63*, 1780.
36. Oscarson, S.; Sehgelmeble, F. W., *J. Am. Chem. Soc.* **2000**, *122*, 8869.
37. Bhattacharya, S. K.; Danishefsky, S. J., *J. Org. Chem.* **2000**, *65*, 144.
38. Zhang, Z. H.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H., *J. Am. Chem. Soc.* **1999**, *121*, 734.
39. Ye, X. S.; Wong, C. H., *J. Org. Chem.* **2000**, *65*, 2410.
40. Mehta, S.; Whitfield, D. M., *Tetrahedron* **2000**, *56*, 6415.
41. Åberg, P. M.; Blomberg, L.; Lönn, H.; Norberg, T., *J. Carbohydr. Chem.* **1994**, *13*, 141.
42. Blomberg, L.; Norberg, T., *J. Carbohydr. Chem.* **1992**, *11*, 751.
43. Veeneman, G. H.; van Boom, J. H., *Tetrahedron Lett.* **1990**, *31*, 275.
44. Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H., *Tetrahedron Lett.* **1990**, *31*, 1331.
45. Roy, R.; Andersson, F. O.; Letellier, M., *Tetrahedron Lett.* **1992**, *33*, 6053.
46. Cao, S. D.; Hernández-Matéo, F.; Roy, R., *J. Carbohydr. Chem.* **1998**, *17*, 609.
47. Sliedregt, L. A. J. M.; Zegelaar-Jaarsveld, K.; van der Marel, G. A.; van Boom, J. H., *Synlett* **1993**, 335.
48. Kanemitsu, T.; Kanie, O.; Wong, C. H., *Angew. Chem., Int. Ed.* **1998**, *37*, 3415.
49. Marra, A.; Gauffeny, F.; Sinaÿ, P., *Tetrahedron* **1991**, *47*, 5149.
50. Marra, A.; Sinaÿ, P., *Carbohydr. Res.* **1990**, *195*, 303.
51. Fügedi, P.; Garegg, P. J.; Oscarson, S.; Rosen, G.; Silwanis, B. A., *Carbohydr. Res.* **1991**, *211*, 157.
52. Chenault, H. K.; Castro, A.; Chafin, L. F.; Yang, J., *J. Org. Chem.* **1996**, *61*, 5024.
53. Garegg, P. J.; Hansson, J.; Helland, A. C.; Oscarson, S., *Tetrahedron Lett.* **1999**, *40*, 3049.
54. Sugimura, H.; Muramoto, I.; Nakamura, T.; Osumi, K., *Chem. Lett.* **1993**, 169.
55. Sugimura, H.; Sujino, K., Jpn. Kokai Tokkyo Koho JP 10 182,691 (*Chem. Abstr.* **1998**, *129*, 149179e).
56. Sugimura, H., Jpn. Kokai Tokkyo Koho JP 10 237,090 (*Chem. Abstr.* **1998**, *129*, 245422z).
57. Hasegawa, A.; Murase, T.; Ogawa, M.; Ishida, H.; Kiso, M., *J. Carbohydr. Chem.* **1990**, *9*, 415.
58. Hällgren, C., *J. Carbohydr. Chem.* **1992**, *11*, 527.
59. Lipták, A.; Szabó, L., *Carbohydr. Res.* **1988**, *184*, C5–C8.
60. Chernyak, A. Y.; Antonov, K. V.; Kochetkov, N. K., *Bioorg. Khim.* **1989**, *15*, 1113 (*Chem. Abstr.* **1990**, *112*, 158760p).
61. Kunz, H.; Wernig, P.; Schultz, M., *Synlett* **1990**, 631.
62. (a) Bernlind, C.; Bennett, S.; Oscarson, S., *Tetrahedron: Asymmetry* **2000**, *11*, 481. (b) Ernst, B.; Wagner, B.; Baisch, G.; Katapodis, A.; Winkler, T.; Öhrlein, R., *Can. J. Chem.* **2000**, *78*, 892. (c) Thoma, G.; Magnani, J. L.; Patton, J. T., *Bioorg. Med. Chem. Lett.* **2001**, *11*, 923.
63. Drinnan, N.; West, M. L.; Broadhurst, M.; Kellam, B.; Toth, I., *Tetrahedron Lett.* **2001**, *42*, 1159.
64. Lear, M. J.; Yoshimura, F.; Hirama, M., *Angew. Chem. Int. Ed.* **2001**, *50*, 946.
65. Alpe, M.; Oscarson, S.; Svahnberg, P., *J. Carbohydr. Chem.* **2004**, *23*, 403.
66. (a) Marinier, A.; Martel, A.; Bachand, C.; Plamondon, S.; Turmel, B.; Daris, J.-P.; Banville, J.; Lapointe, P.; Ouellet, C.; Dextraze, P.; Menard, M.; Wright, J. J. K.; Alford, J.; Lee, D.; Stanley, P.; Nair, X.; Todderud, G.; Tramposch, K. M., *Bioorg. Med. Chem.* **2001**, *9*, 1395. See also (b) Plettenburg, O.; Bodmer-Narkevitch, V.; Wong, C.-H., *J. Org. Chem.* **2002**, *67*, 4559.
67. Ziegler, T.; Dettman, R.; Zettl, A.; Zettl, U., *J. Carbohydr. Chem.* **1999**, *18*, 1079.
68. Ikeda, K.; Konishi, K.; Sano, K.; Tanaka, K., *Chem. Pharm. Bull.* **2000**, *48*, 163.

cis-3-[*N*-(3,5-Dimethylphenyl)benzenesulfonamido]borneol[1]



(1*R*) (*endo,endo*)

[87360-02-9] $C_{24}H_{31}NO_3S$ (MW 413.63)

InChI = 1/C24H31NO3S/c1-16-13-17(2)15-18(14-16)25(29
(27,28)19-9-7-6-8-10-19)21-20-11-12-24(5,22(21)26)23
(20,3)4/h6-10,13-15,20-22,26H,11-12H2,1-5H3/
t20-,21+,22+,24+/m1/s1

InChIKey = XOYOZKHVKVMVIE-VCHRRKICBU

(chiral auxiliary; ester enolate derivatives undergo stereoselective alkylations[2] and enantioselective *anti*-aldol reactions;[3] enoate derivatives undergo stereoselective 1,4-conjugate additions of organocopper reagents[4])

Alternate Name: *N*-(3,5-dimethylphenyl)-*N*-(3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl)benzenesulfonamide.

Physical Data: (1*R*) (*endo,endo*): mp 147–150 °C; $[\alpha]_D^{20}$ −26.0° (*c* = 4.0, $CHCl_3$).

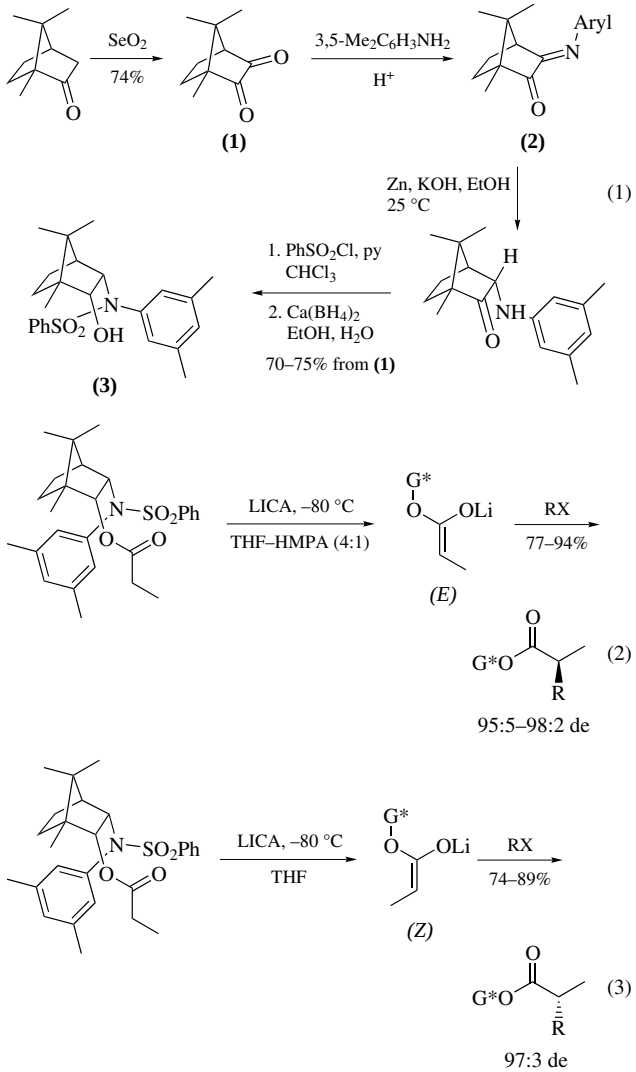
Handling, Storage, and Precautions: the auxiliary is stable indefinitely at ambient temperatures in a sealed container.

Introduction. One of several auxiliaries that exploit the asymmetry of naturally occurring (+)-camphor, the 3-(*N*-(3,5-dimethylphenyl)benzenesulfonamido)borneol auxiliary has proven significant utility in the π-facial differentiation of ester enolates and enoate derivatives. The *endo* orientation of the C(2) and C(3) substituents places the reactive functionality within the concave pocket created by the bornane skeleton as well as the shielding ability of the *N*-arylbenzenesulfonamide.

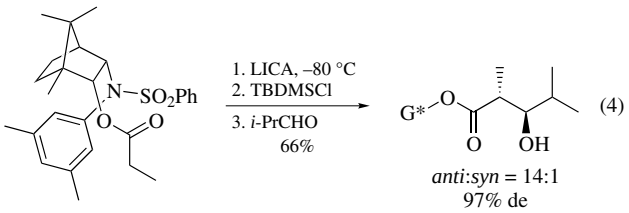
Preparation of the Auxiliary. A synthesis of the (1*R*) auxiliary has been reported starting from (+)-camphor (eq 1). Zinc reduction of the intermediate imine (**2**) followed by sulfonylation and ketone reduction with $Ca(BH_4)_2$ afforded the *cis,endo* product in 70–75% overall yield from camphorquinone (**1**).

Preparation of Derivatives. Enoate derivatives were prepared by Horner–Wittig reactions between aldehydes and the ethyl phosphonate derived from the chloroacetyl ester of (**3**) in high (*E*) selectivity (97:3).[4b] Ester derivatives were obtained by treating alcohol (**3**) with the corresponding carboxylic acid chloride.[5]

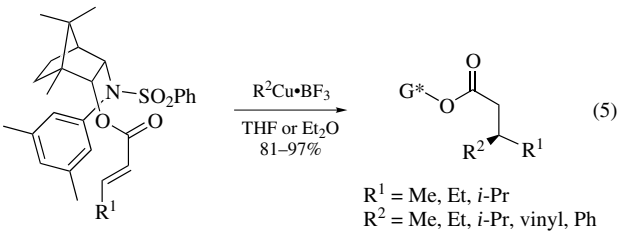
α-Alkylation of Ester Derivatives.[2] Alkylation of ester enolate derivatives, prepared by metalation with lithium cyclohexylisopropylamide (LICA), proceeds with high stereoselectivity. The configuration of the product is dependent on the solvent employed (eqs 2 and 3). When performed in THF with the addition of HMPA the product with the (*S*) configuration was formed preferentially; however, without HMPA the (*R*) configuration predominated. Silyl chloride trapping studies suggest that in the presence of HMPA the (*E*)-ester enolate is stereoselectively formed, as opposed to the (*Z*)-ester enolate in THF alone.[2b] The stereochemical outcome has been explained by alkylation of the corresponding enolate π-face opposite to the shielding 3,5-dimethylphenyl moiety. *O*-Benzylglycolates have also been employed in stereoselective alkylations, affording diastereomeric excesses of 88–95%.[2c] In this case the solvent-dependent stereochemical reversal does not occur and the (*E*)-ester enolate is stereoselectively formed in both cases.



Aldol Reactions of Ester Derivatives.[3] The titanium(IV) chloride-catalyzed addition of aldehydes to *O*-silyl ketene acetals derived from acetate and propionate esters proceeds with high stereoselectivity. Formation of the silyl ketene acetal was found to be essential for high diastereoselectivity. Treatment of the silyl ketene acetal, derived from deprotonation of the acetate ester with LICA in THF and silyl trapping, with a corresponding aldehyde in the presence of $TiCl_4$ (1.1 equiv) afforded the addition products in 93:7 diastereoselectivity and moderate yield (51–67%). Similarly, the propionate ester provides the *anti*-aldol product in high *anti*/*syn* selectivity (14:1) and facial selectivity (eq 4).



1,4-Conjugate Additions to Enoate Derivatives.[4] High diastereoselectivity has been observed for boron trifluoride-promoted addition of alkyl and aryl organocopper reagents to enoate derivatives (eq 5).[4b] When the organocopper reagent was prepared from alkyl- or aryllithiums, diethyl ether was found to be the solvent of choice; however, with Grignard reagents, THF was superior. The addition of boron trifluoride exhibited little influence on reactivity of the copper reagent but did enhance the stereoselectivity of the addition. It is believed that the enoate adopts an *s-trans* conformation and the observed stereochemical preference results from approach of the organocopper reagent to the less sterically hindered face opposite the aryl moiety.



Nondestructive Removal of the Auxiliary. Primary alcohols are obtained by lithium aluminum hydride reduction of the corresponding chiral esters. Also, hydrolysis of the auxiliary under basic conditions, 2N KOH in methanol,.[4b] provides the carboxylic acid and recovered alcohol (**3**).

Related Reagents. 3-Hydroxyisoborneol; (1*R*,2*S*)-*N*-Methylephedrine.

1. Oppolzer, W., *Tetrahedron* **1987**, *43*, 1969.
2. (a) Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A., *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 207. (b) Helmchen, G.; Selim, A.; Dorsch, D.; Taufer, I., *Tetrahedron Lett.* **1983**, *24*, 3213. (c) Helmchen, G.; Wierzchowski, R., *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 60.
3. Helmchen, G.; Leifauf, U.; Taufer-Knöpfel, I., *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874.
4. (a) Rossiter, B.; Swingle, N. M., *Chem. Rev.* **1992**, *92*, 771. (b) Helmchen, G.; Wegner, G., *Tetrahedron Lett.* **1985**, *26*, 6051.
5. Dorsch, D.; Kunz, E.; Helmchen, G., *Tetrahedron Lett.* **1985**, *26*, 3319.

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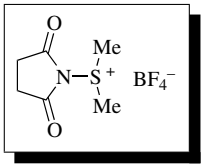
Dimethylsuccinimidosulfonium Tetrafluoroborate



[54884-50-3] $C_6H_{10}BF_4NO_2S$ (MW 247.02)

InChI = 1/C6H10NO2S.BF4/c1-10(2)7-5(8)3-4-6(7)9;2-1(3,4)5/h3-4H2,1-2H3;/q+1;-1

InChIKey = YOOBTKIVSIZFRY-UHFFFAOYAF

(stable sulfonium salt for the mild oxidation of alcohols and catechols in the presence of a tertiary amine; also used for the introduction of a methylthiomethylene substituent in the *ortho* position of simple phenols, or the transfer of a dimethylsulfonium group to nucleophiles)

Alternate Name: succinimidodimethylsulfonium tetrafluoroborate.

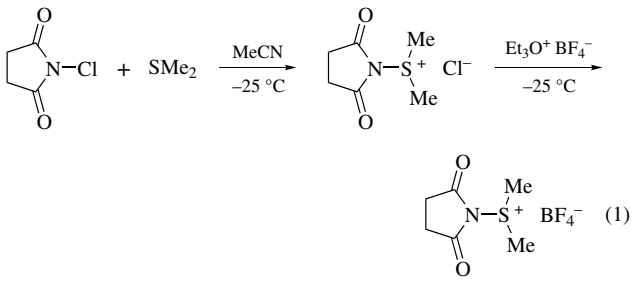
Physical Data: mp 169–171 °C

Solubility: very sol methylene chloride, acetonitrile; insol ether.

Form Supplied in: colorless solid; not commercially available.

Analysis of Reagent Purity: mp, ^{1}H NMR, or elemental analysis.

Preparative Methods: an acetonitrile solution of *N*-Chlorosuccinimide and dimethyl sulfide produces the unstable dimethylsuccinimidosulfonium chloride at −25 °C, which is then treated with triethyloxonium tetrafluoroborate (eq 1).



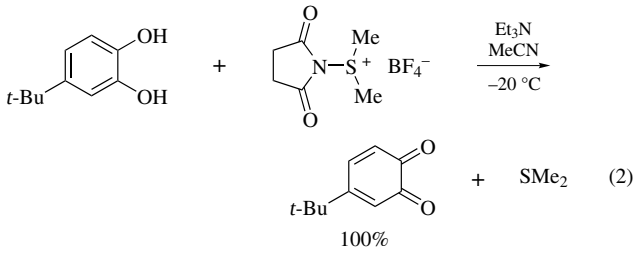
Handling, Storage, and Precautions: hygroscopic, but thermally and air stable; can be stored indefinitely under N_2 in sealed flasks in the absence of moisture.

Introduction. The general class of dimethylsuccinimidosulfonium salts are reagents useful for the transfer of the dimethylsulfonium moiety to nucleophilic species.[1] The main variation in this group of reagents is the nature of the counteranion (Cl, Br, BF_4). The title reagent incorporating the tetrafluoroborate anion is a thermally stable and isolable salt of this series. Both the chloride and bromide are generally generated in situ for the purpose of oxidations of alcohols[2] or the sulfonium aminations of anilines.[3]

Experimental Procedure. NCS (22.7 g, 0.17 mol) was dissolved in freshly distilled acetonitrile under a nitrogen atmosphere. The solution was cooled to −25 °C with stirring while 10 mL (0.2 mol) of DMS was added dropwise. After stirring for

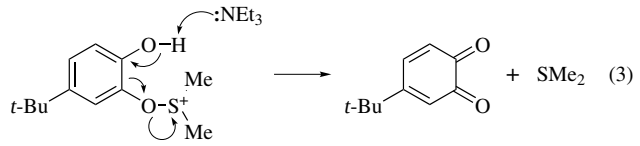
15 min, the reaction mixture was cooled to −50 °C until crystals formed. A solution of 25 g (0.17 mol) of triethyloxonium tetrafluoroborate in 100 mL of acetonitrile was added dropwise to the reaction mixture. After addition was complete (about 1 h), the flask was cooled to −78 °C until the solution solidified. The solid mass was slowly brought to rt over a period of 4 h; then 500 mL of anhyd ether was added slowly to precipitate the dimethylsuccinimidosulfonium tetrafluoroborate as a white solid. Recrystallization from acetonitrile/ether gave 33.6 g (80%) of the product as white needles (mp 169–171 °C).

Oxidation Reactions. The advantage of the stable tetrafluoroborate reagent lies in its stoichiometric use in a variety of solvents under controlled reaction conditions in the absence of a nucleophilic anion. A particularly mild and selective oxidation of catechols to *o*-quinones can be effected with the title reagent and 1 equiv of triethylamine in acetonitrile below 0 °C (eq 2).



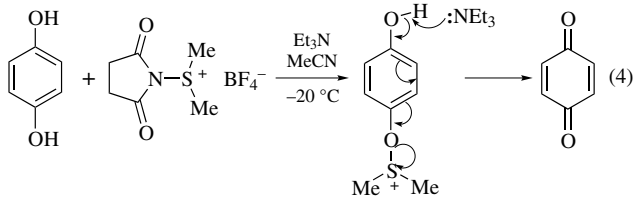
(2)

These oxidations can be carried out between −20 and −50 °C in order to extend the lifetime of the sensitive and very reactive *o*-quinones.[4] The mechanism of this oxidation process involves the intermediacy of an aryloxysulfonium cation which undergoes base-promoted elimination of dimethyl sulfide (eq 3). The merits of this procedure include the absence of deleterious byproducts which could react with the quinone product and the lack of opportunity for overoxidation.



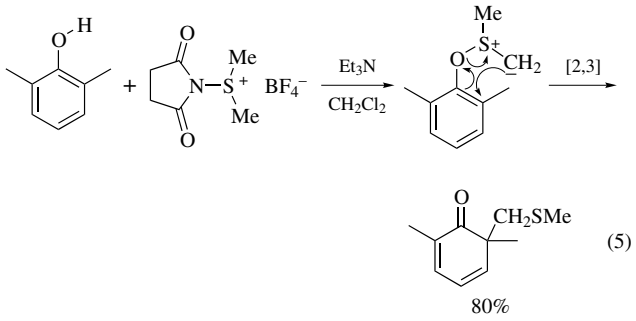
(3)

The title reagent is also effective for the oxidation of *p*-hydroquinones to *p*-quinones in quantitative yields (eq 4). The employment of an amine base is essential for this oxidation process.



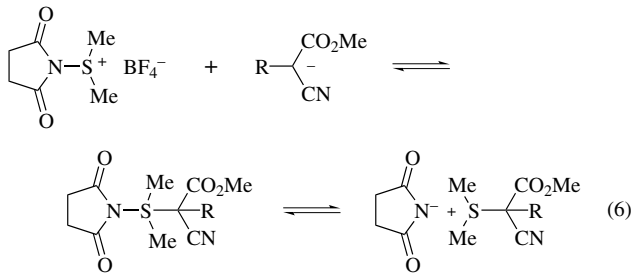
(4)

Nucleophilic Additions to Succinimidosulfonium Cations. The title reagent can also be considered as a source of the dimethylsulfonium cation through reaction with nucleophiles. Thus the nucleophilic addition of a phenolic oxygen atom to the reagent leads to an intermediate aryloxysulfonium species, which rapidly gives up a proton to generate a sulfonium ylide.[5] This latter intermediate undergoes a facile [2,3]-sigmatropic rearrangement to produce cyclohexadienones with 2,6-disubstituted phenols (eq 5).[6] In the case of unsubstituted phenols, the sigmatropic rearrangement takes place and the dienone rearomatizes to give the *ortho*-methylthiomethylene phenol.[7]

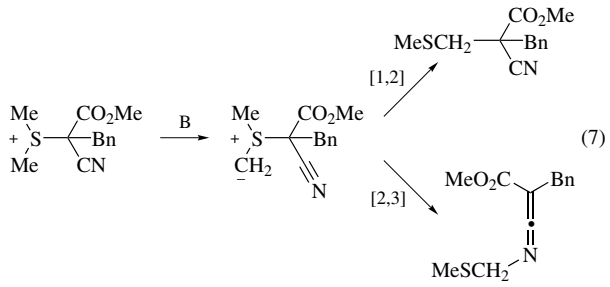


(5)

Other heteroatoms such as nitrogen and sulfur behave as good nucleophiles in reactions with the title reagent and related salts.[8] Stabilized carbanions such as substituted α-cyanoacetates react readily with the succinimidosulfonium reagent to give several rearrangement products.[8] The initial combination of the reagent with the cyanoacetate anion is thought to generate a σ-sulfurane intermediate which could ionize to form the succinimido anion and a sulfonium cation (eq 6). In the presence of a weak base, the sulfonium cation is deprotonated to an ylide which can undergo a [1,2]-rearrangement to a methylthiomethylene derivative of the starting carbanion or, alternatively, the ylide may undergo a [2,3]-sigmatropic rearrangement to yield a substituted ketenimine (eq 7). In most cases, the ketenimine is the major product.



(6)



(7)

1. For a review of sulfur-containing cations, see: Marino, J. P. *Topics in Sulfur Chemistry*; Senning, A., Ed.; Thieme: Stuttgart, 1976; Vol. 1.
2. Corey, E. J.; Kim, C. U., *J. Am. Chem. Soc.* **1972**, *94*, 7586.
3. Gassman, P. G.; van Bergen, T. J., *J. Am. Chem. Soc.* **1973**, *95*, 2718, 591, 590.
4. (a) Marino, J. P.; Schwartz, A., *J. Chem. Soc., Chem. Commun.* **1974**, 812. (b) Schwartz, A., PhD thesis, *The Design of Specific Oxidants for Phenolic Compounds: Applications to the Isoquinoline Alkaloids*; The University of Michigan, 1978.

5. Pfitzner, K. E.; Marino, J. P.; Olofson, R. A., *J. Am. Chem. Soc.* **1965**, *87*, 4658.
6. Quinkert, G.; Duerner, G.; Kleiner, E.; Adam, F.; Haupt, E.; Liebfritz, D., *Chem. Ber.* **1980**, *113*, 2227.
7. (a) Marino, J. P.; Pfitzner, K. E.; Olofson, R. A., *Tetrahedron* **1971**, *27*, 4181. (b) Olofson, R. A.; Marino, J. P., *Tetrahedron* **1971**, *27*, 4195.
8. Morel, G.; LeMoing-Orliac, M. A.; Khamsitthideth; S., Foucaud, A., *Tetrahedron* **1982**, *38*, 527.

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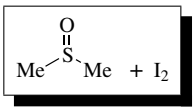
Dimethyl Sulfoxide–Iodine



(DMSO)
[67-68-5] C_2H_6OS (MW 78.13)
InChI = 1/C2H6OS/c1-4(2)3/h1-2H3
InChIKey = IAZDPXIOMUYVGZ-UHFFFAOYAR
(I_2)
[7553-56-2] I_2 (MW 253.81)
InChI = 1/I2/c1-2
InChIKey = PNDPGZBMCMUPRI-UHFFFAOYAF

(oxidant with diverse applicability, including the conversion of benzoyl methylene groups to di- and triketones, thioacetals to carbonyl compounds, and ketones to α,β-unsaturated ketones)

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. I_2: mp 113 °C; bp 184 °C; *d* 4.930 g cm^{-3}.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. I_2: sol ether, $CHCl_3$, CS_2, aq soln HI.

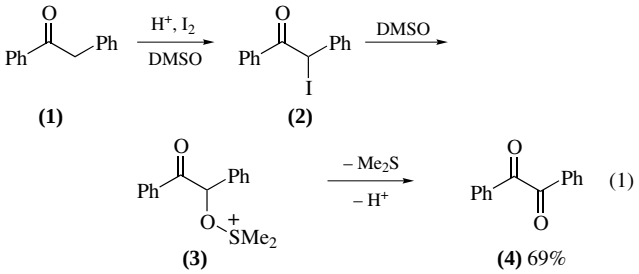
Form Supplied in: DMSO is a colorless liquid; widely available, including 'anhydrous' grades of 99%+ DMSO packed under N_2. I_2 is a widely available crystalline solid.

Preparative Methods: the actual reagent may differ from one reaction to another, and the specific procedures also differ.

Purification: DMSO: distillation from calcium hydride at 56–57 °C/5 mmHg[1a] or 83–85 °C/17 mmHg;[1b] storage over 3Å molecular sieves. I_2: sublimation.

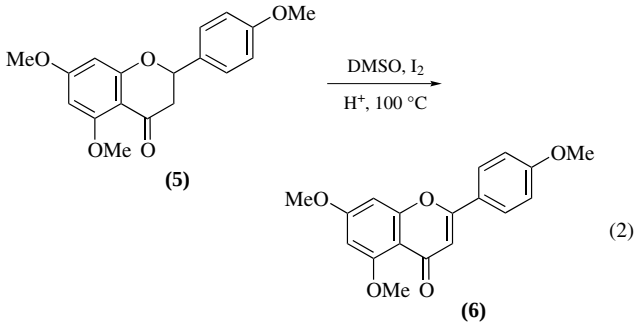
Handling, Storage, and Precautions: Dimethyl sulfoxide is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench) and dimethyl sulfone above 90 °C;[1c] Iodine is corrosive and toxic.

The formation of dicarbonyl compounds by this reagent is a variation of the Kornblum oxidation[2] and presumably involves acid-catalyzed iodination of the carbonyl compound (**1**) to give an α-iodo ketone (**2**) which undergoes displacement by DMSO to give an alkoxysulfonium ion (**3**); this gives a dicarbonyl compound (**4**) in a 1,2-elimination with assistance by base (eq 1).[3a]

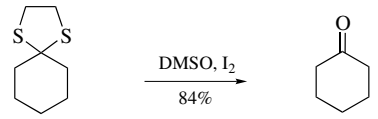


(1)

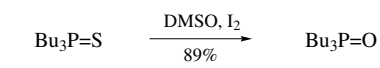
Reaction of the flavanone (**5**) to give (**6**) presumably involves an α-iodo ketone which undergoes elimination (eq 2).[3b] The ethylene thioacetal of cyclohexanone gives cyclohexanone (eq 3),[3c] and phosphine sulfides and selenides give the oxo analogs (eq 4).[3d]



(2)



(3)



(4)

Related Reagents. Dimethyl Sulfoxide–Acetic Anhydride; Dimethyl Sulfoxide–Dicyclohexylcarbodiimide; Dimethyl Sulfoxide–Methanesulfonic Anhydride; Dimethyl Sulfoxide–Oxalyl Chloride; Dimethyl Sulfoxide–Phosgene; Dimethyl Sulfoxide–Phosphorus Pentoxide; Dimethyl Sulfoxide–Sulfur Trioxide/Pyridine; Dimethyl Sulfoxide–Trifluoroacetic Anhydride; Dimethyl Sulfoxide–Triphosgene.

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1. (a) Iwai, I.; Ide, J., *Org. Synth., Coll. Vol.* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S., *Org. Synth., Coll. Vol.* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M., *Org. Synth., Coll. Vol.* **1973**, *5*, 755.
2. (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M., *J. Am. Chem. Soc.* **1957**, *79*, 6562. (b) Kornblum, N.; Jones, W. J.; Anderson, G. J., *J. Am. Chem. Soc.* **1959**, *81*, 4113. (c) Kilenyi, S. N., *Comprehensive Organic Synthesis* **1991**, *7*, 653.
3. (a) Furukawa, N.; Akasaka, T.; Aida, T.; Oae, S., *J. Chem. Soc., Perkin Trans. 1* **1977**, 372. (b) Fatma, W.; Iqbal, J.; Ismail, H.; Ishratullah, K.; Shaida, W. A.; Rahman, W., *Chem. Ind. (London)* **1979**, 315. (c) Chattopadhyaya, J. B.; Rao, A. V. R., *Tetrahedron Lett.* **1973**, 3735. (d) Mikolajczyk, M.; Luczak, J., *Synthesis* **1975**, 114.

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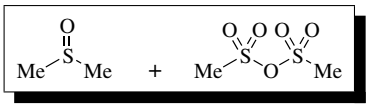
Dimethyl Sulfoxide–Methanesulfonic Anhydride[1]



(DMSO)
[67-68-5] C_2H_6OS (MW 78.13)
InChI = 1/C2H6OS/c1-4(2)3/h1-2H3
InChIKey = IAZDPXIOMUYVGZ-UHFFFAOYAR
(Ms_2O)
[7143-01-3] $C_2H_6O_5S_2$ (MW 174.20)
InChI = 1/C2H6O5S2/c1-8(3,4)7-9(2,5)6/h1-2H3
InChIKey = IZDROVVXIHRYMH-UHFFFAOYAS

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; suitable for large-scale oxidation; gives good yields with minimal amounts of byproduct methylthiomethyl ethers)

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. Ms_2O: mp 69–70 °C; bp 125 °C/4 mmHg.

Solubility: DMSO: sol H_2O, alcohol, acetone, CH_2Cl_2, THF. Ms_2O: reacts H_2O; sol CH_2CH_2, THF.

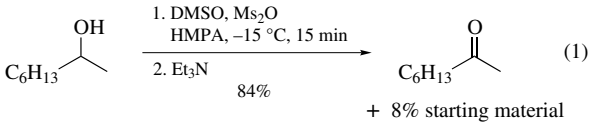
Form Supplied in: DMSO is a colorless liquid that is widely available, including 'anhydrous' grades of 99+% purity packed under N_2; Ms_2O is a crystalline solid that is widely available.

Preparative Method: the active oxidant is presumably Me_2^+SOMs, and is generated in situ by adding Ms_2O to the alcohol in DMSO–HMPA.

Purification: DMSO: distillation from calcium hydride at 56–57 °C/5 mmHg,[2a] or 83–85 °C/17 mmHg;[2b] storage over 3Å molecular sieves.

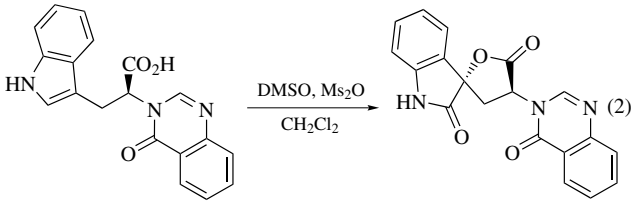
Handling, Storage, and Precautions: Dimethyl sulfoxide is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench) and dimethyl sulfone above 90 °C;[2c] methanesulfonic anhydride is corrosive and moisture-sensitive.

DMSO–Ms_2O is occasionally used for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, and gives good yields of products with minimal formation of byproducts (eq 1).[3a,b] The use of the toxic hexamethylphosphoric triamide in some procedures is a disadvantage.[3a,b]



(1)

Reaction of the L-tryptophan derivative (**1**) with DMSO–Ms_2O gave **2** (eq 2).[3c]



(1) **(2)**

Related Reagents. *N*-Chlorosuccinimide–Dimethyl Sulfide; Chromic Acid; Dimethyl Sulfide–Chlorine; Dimethyl Sulfoxide–Acetic Anhydride; Dimethyl Sulfoxide–Dicyclohexylcarbodiimide; Dimethyl Sulfoxide–Oxalyl Chloride; Dimethyl Sulfoxide–Phosphorus Pentoxide; Dimethyl Sulfoxide–Sulfur Trioxide/Pyridine; Dimethyl Sulfoxide–Trifluoroacetic Anhydride; Dimethyl Sulfoxide–Triphosgene; Manganese Dioxide; Pyridinium Chlorochromate; Pyridinium Dichromate; Ruthenium(IV) Oxide; Silver(I) Carbonate on Celite; 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one.

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1. (a) Tidwell, T. T., *Org. React.* **1990**, *39*, 297. (b) Tidwell, T. T., *Synthesis* **1990**, 857. (c) Lee, T. V., *Comprehensive Organic Synthesis* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: New York, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, 1990. (e) Mancuso, A. J.; Swern, D., *Synthesis* **1981**, 165.

2. (a) Iwai, I.; Ide, J., *Org. Synth., Coll. Vol.* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S., *Org. Synth., Coll. Vol.* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M., *Org. Synth., Coll. Vol.* **1973**, *5*, 755.

3. (a) Omura, K.; Swern, D., *Tetrahedron* **1978**, *34*, 1651. (b) Albright, J. D., *J. Org. Chem.* **1974**, *39*, 1977. (c) Büchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y., *J. Am. Chem. Soc.* **1979**, *101*, 5084.

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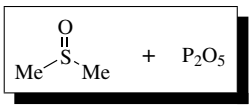
Dimethyl Sulfoxide–Phosphorus Pentoxide[1]



(DMSO)
[67-68-5] C_2H_6OS (MW 78.13)
InChI = 1/C2H6OS/c1-4(2)3/h1-2H3
InChIKey = IAZDPXIOMUYVGZ-UHFFFAOYAR
(P_2O_5)
[1314-56-3] O_5P_2 (MW 141.95)
InChI = 1/O5P2/c1-6(2)5-7(3)4
InChIKey = YWEUIGNSBFLMFL-UHFFFAOYAH

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; modified procedure gives very good yields with short reaction times at 0 °C with minimal formation of byproducts; inexpensive)

Alternate Name: Onodera reagent.

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. P_2O_5: sublimes 360 °C/760 mmHg.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. P_2O_5: sol H_2O.

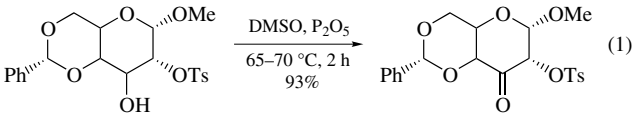
Form Supplied in: DMSO is a colorless liquid; widely available, including 'anhydrous' grades of DMSO packed under N_2; P_2O_5 (more accurately P_4O_{10}) is a white crystalline solid; widely available.

Preparative Method: the active oxidant, formulated as Me_2+:SO(P_2O_5)$^-$, is generated in situ from the reaction of DMSO and P_2O_5 in the presence of the alcohol.

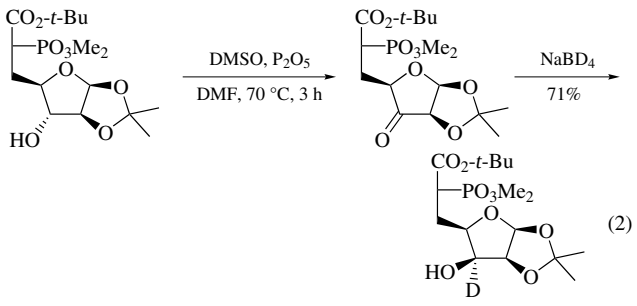
Purification: DMSO: distillation from CaH_2 at 56–57 °C/5 mmHg[2a] or 83–85 °C/17 mmHg;[2b] storage over 3Å molecular sieves. P_2O_5: sublimation.

Handling, Storage, and Precautions: Dimethyl sulfoxide is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench) and dimethyl sulfone above 90 °C;[2c] Phosphorus(V) oxide is corrosive and a strong desiccant.

DMSO–P_2O_5 has long been used,[3a] but the early procedures involved elevated temperatures with no added base, and required long reaction times, as in the example of eq 1.[3b] This procedure has been used in conjunction with a reduction step for the inversion of hydroxy group configuration (eq 2).[3c] More recently the addition of triethylamine base permits shorter reaction times and lower temperatures, but dry ice temperatures are not required, and this can be an advantage relative to the use of dimethyl sulfoxide–oxalyl chloride (eq 3).[4] The DMSO and P_2O_5 react to form $Me_2^+SO(P_2O_5)^-$, which reacts in situ with the alcohol ROH to give the alkoxysulfonium ion $Me_2^+SOR^-$ common to most oxidations by activated DMSO.



(1)



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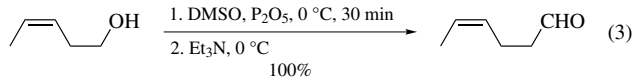

(3)

Related Reagents. *N*-Chlorosuccinimide–Dimethyl Sulfide; Chromic Acid; Dimethyl Sulfide–Chlorine; Dimethyl Sulfoxide–Acetic Anhydride; Dimethyl Sulfoxide–Dicyclohexylcarbodiimide; Dimethyl Sulfoxide–Methanesulfonic Anhydride; Dimethyl Sulfoxide–Oxalyl Chloride; Dimethyl Sulfoxide–Sulfur Trioxide/Pyridine; Dimethyl Sulfoxide–Trifluoroacetic Anhydride; Dimethyl Sulfoxide–Triphosgene; Manganese Dioxide; Pyridinium Chlorochromate; Pyridinium Dichromate; Ruthenium(IV) Oxide; Silver(I) Carbonate on Celite; 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one.

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1. (a) Tidwell, T. T., *Org. React.* **1990**, *39*, 297. (b) Tidwell, T. T., *Synthesis* **1990**, 857. (c) Lee, T. V., *Comprehensive Organic Synthesis* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: London, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, 1990. (f) Mancuso, A. J.; Swern, D., *Synthesis* **1981**, 165. (g) Moffatt, J. G. In *Oxidation*; Augustine, R. L.; Trecker, D. J.; Eds.; Dekker: New York, 1971; Vol. 2, Chapter 1.
2. (a) Iwai, I.; Ide, J., *Org. Synth., Coll. Vol.* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S., *Org. Synth., Coll. Vol.* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M., *Org. Synth., Coll. Vol.* **1973**, *5*, 755.
3. (a) Onodera, K.; Hirano, S.; Kashimura, N., *J. Am. Chem. Soc.* **1965**, *87*, 4651. (b) Jones, G. H.; Moffatt, J. G. In *Methods in Carbohydrate Chemistry*; Whistler, R. L.; BeMiller, J. N., Eds; Academic: New York, **1972**; Vol. 6, p 315. (c) Moore, B. S.; Cho, H.; Casati, R.; Kennedy, E.; Reynolds, K. A.; Mocek, U.; Beale, J. M.; Floss, H. G., *J. Am. Chem. Soc.* **1993**, *115*, 5254.
4. (a) Taber, D. F.; Amedio, J. C., Jr.; Jung, K.-Y., *J. Org. Chem.* **1987**, *52*, 5621. (b) Taber, D. F.; Amedio, J. C., Jr.; Raman, K., *J. Org. Chem.* **1988**, *53*, 2984.

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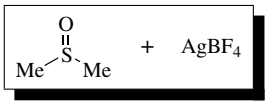
Dimethyl Sulfoxide–Silver Tetrafluoroborate



(DMSO)
[67-68-5] C_2H_6OS (MW 78.13)
InChI = 1/C2H6OS/c1-4(2)3/h1-2H3
InChIKey = IAZDPXIOMUYVGZ-UHFFFAOYAR
($AgBF_4$)
[14104-20-2] BF_4Ag (MW 194.68)
InChI = 1/Ag.BF4/c;2-1(3,4)5/q+1;-1
InChIKey = CCAVYRRHZLAMDJ-UHFFFAOYAH

(reagent for conversion of alkyl halides to aldehydes and ketones)

Physical Data: DMSO: mp 18.55 °C; bp 189 °C/760 mmHg; 76 °C/16 mmHg; *d* (25 °C) 1.0958 g cm^{-3}; dielectric constant (25 °C) 46.7. $AgBF_4$: mp 200 °C.

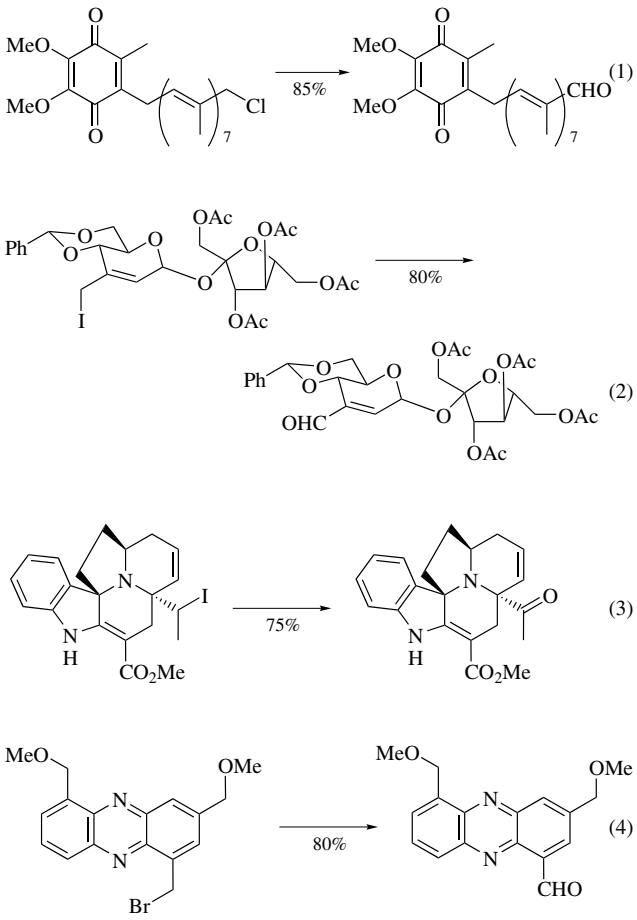
Solubility: DMSO: miscible with water and most organic solvents. $AgBF_4$: sol water, ether, toluene, nitromethane, DMSO; moderately sol benzene and cyclohexane.

Form Supplied in: DMSO: clear anhyd liquid, widely available. $AgBF_4$: crystalline white solid, widely available.

Drying: DMSO: generally quite dry when freshly opened, but very hygroscopic; distill from CaH_2 under reduced pressure. $AgBF_4$: very hygroscopic; dry in vacuo at 80 °C.

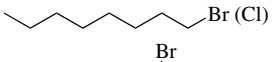
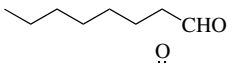
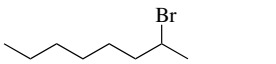
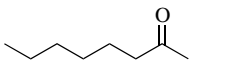
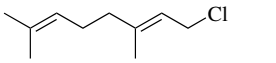
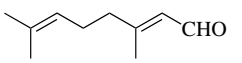
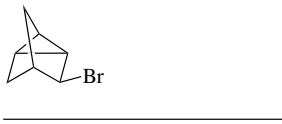
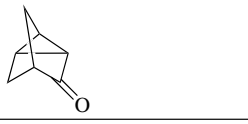
Handling, Storage, and Precautions: see dimethyl sulfoxide and silver(I) tetrafluoroborate.

Silver-assisted nucleophilic displacement of halide to form an alkoxysulfonium ion, followed by deprotonation, most commonly by triethylamine,[1] effectively converts benzylic and allylic halides and some primary[1b] and secondary alkyl halides[1a,b,f,5] to the corresponding aldehydes or ketones at room temperature (eq 1,[1d] eq 2,[1e] eqs eq 3,[1f] and eq 4[1j]). While avoiding the higher temperatures generally required by the Kornblum method[2] ($NaHCO_3$ (+NaI[3]), DMSO, 100–150 °C), the silver-assisted reaction has the disadvantage of higher cost. Most oxidations have been accomplished with silver tetrafluoroborate; however, there are successful examples which used silver(I) nitrate[4] or hexafluorophosphate.[5] The same type of conversion has been accomplished with trialkylamine oxides,[6] ion-exchange polymer-bound chromate ion,[7] the classical Sommelet reaction,[8] and other methods.[9] Oxidation of the corresponding alcohols is the obvious alternative.[1e,k,] On the other hand, bromination of an allylic or benzylic methyl group with *N*-bromosuccinimide followed by DMSO–$AgBF_4$ oxidation[1h,i,j] is a useful substitute for direct oxidation of the hydrocarbon.[10]



Typically, a solution of 1 mmol of halide (usually bromide or iodide) and 1.1–2.0 mmol of silver salt in 1–5 mL of DMSO is stirred at rt for 10 min to 24 h. Excess triethylamine is then added, the mixture is stirred for an additional 15 min and diluted with water. The product is isolated in the usual fashion. Several examples are given in Table 1.[1a,1b]

Table 1 Syntheses Employing DMSO–$AgBF_4$

Halide	Product	Yield (%)
		83 (0) [1b]
		80 [1b]
		90 [1b]
		69 [1a]

1. (a) Lemal, D. M.; Fry, A. J., *J. Org. Chem.* **1964**, *29*, 1673. (b) Ganem, B.; Boeckman, R. K., Jr., *Tetrahedron Lett.* **1974**, 917. (c) Roedig, A.; Fouré, M.; Försch, M., *Chem. Ber.* **1977**, *110*, 322. (d) Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H., *J. Chem. Soc., Perkin Trans. 1* **1978**, 1101. (e) Fraser-Reid, B.; Iley, D. E., *Can. J. Chem.* **1979**, *57*, 645. (f) Langlois, N.; Andriamialisoa, R. Z., *J. Org. Chem.* **1979**, *44*, 2468. (g) Tyrell, J. A., III; McEwen, W. E., *J. Org. Chem.* **1981**, *46*, 2476. (h) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L., *J. Org. Chem.* **1981**, *46*, 4825. (i) Nagao, Y.; Yamada, S.; Fujita, E., *Tetrahedron Lett.* **1983**, *24*, 2291. (j) Liu, W.-C.; Parker, W. L.; Brandt, S. S.; Atwal, K. S.; Ruby, E. P., *J. Antibiot.* **1984**, *37*, 1313. (k) Frei, B.; Huxley, P.; Maienfisch, P.; Mereyala, H. B.; Rist, G.; O'Sullivan, A. C., *Helv. Chim. Acta* **1990**, *73*, 1905.
2. (a) Kornblum, N.; Jones, W. J.; Anderson, G. J., *J. Am. Chem. Soc.* **1959**, *81*, 4113. (b) Review: Epstein, W. W.; Sweat, F. W., *Chem. Rev.* **1967**, *67*, 247. (c) See also Tidwell, T. T., *Synthesis* **1990**, 857. (d) Mancuso, A. J.; Swern, D., *Synthesis* **1981**, 165.
3. Dave, P.; Byun, H.-S.; Engel, R., *Synth. Commun.* **1986**, *16*, 1343.
4. Ghera, E.; Plemenitas, A.; Ben-David, Y., *Synthesis* **1984**, 504.
5. Raucher, S., *Tetrahedron Lett.* **1978**, *26*, 2261.
6. See, for example,(a) Godfrey, A. G.; Ganem, B., *Tetrahedron Lett.* **1990**, *31*, 4825. (b) Griffith, W. P.; Jolliffe, J. M.; Ley, S. V.; Springhorn, K. F.; Tiffin, P. D., *Synth. Commun.* **1992**, *22*, 1967.
7. Cardillo, G.; Orena, M.; Sandri, S., *Tetrahedron Lett.* **1976**, *44*, 3985.
8. (a) Angyal, S. J., *Org. React.* **1954**, *8*, 197 (Chapter 4). (b) Blažević, N.; Kolbah, D.; Belin, B.; Šunjić, V.; Kajfež, F., *Synthesis* **1979**, 161.
9. (a) Koyama, Y.; Huang, S-P.; Ikeda, D.; Kondo, S., *Synlett* **1990**, 389. (b) Tanaka, H.; Taniguchi, M.; Kameyama, Y.; Yamaguchi, T.; Sasaoka, M.; Shiroi, T.; Torii, S., *Synlett* **1990**, 660. (c) Kilenyi, S. N., *Comprehensive Organic Synthesis*, **1991**, *7*, 653. (d) Larock, R. C., *Comprehensive Organic Transformations*; VCH: New York, 1989; p 599.
10. Ref. 1d, p 591.

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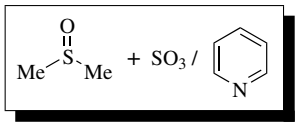
Dimethyl Sulfoxide–Sulfur Trioxide/ Pyridine[1]



(DMSO)
[67-68-5] C_2H_6OS (MW 78.13)
InChI = 1/C2H6OS/c1-4(2)3/h1-2H3
InChIKey = IAZDPXIOMUYVGZ-UHFFFAOYAR
(SO_3)
[7446-11-9] O_3S (MW 80.06)
InChI = 1/O3S/c1-4(2)3
InChIKey = AKEJUJNQAAGONA-UHFFFAOYAX
(SO_3/pyridine)
[26412-87-3] $C_5H_5NO_3S$ (MW 159.16)
InChI = 1/C5H5N.O3S/c1-2-4-6-5-3-1;1-4(2)3/h1-5H;
InChIKey = UDYFLDICVHJSOY-UHFFFAOYAG

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; gives very good yields with short reaction times near rt with minimal formation of byproducts)

Alternate Name: Parikh–Doering reagent.

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. SO_3: mp 16.8 °C; bp 44.7 °C; *d* 1.970 g cm^{-3}. SO_3/pyridine: mp 175 °C.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. SO_3: reacts with H_2O. SO_3/pyridine: sol DMSO; reacts with H_2O.

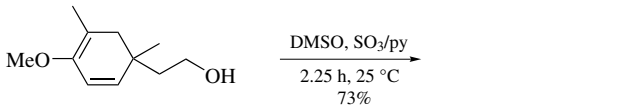
Form Supplied in: DMSO is a colorless liquid; SO_3 is a low-boiling liquid, and the SO_3/pyridine complex is a crystalline solid; widely available, including SO_3/pyridine complex and "anhydrous" grades of DMSO packed under N_2. For the preparation of SO_3/pyridine complex see sulfur trioxide–pyridine.

Preparative Method: the active oxidant, formulated as $Me_2S^+OSO_3^-$,[2d] is generated in situ by mixing DMSO and the SO_3/pyridine complex.

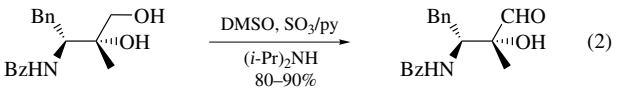
Purification: DMSO: distillation from CaH_2 at 56–57 °C/5 mmHg[2a] or 83–85 °C/17 mmHg;[2b] storage over 3Å molecular sieves.

Handling, Storage, and Precautions: dimethyl sulfoxide is readily absorbed through the skin and should always be handled with gloves in a fume hood; sulfur trioxide and SO_3/pyridine are toxic and corrosive, and react strongly with H_2O; reactions with DMSO form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide and dimethyl sulfone above 90 °C.[2c]

DMSO–SO_3/pyridine[3a] is a convenient oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively. The complex Me_2S^+:OSO_3^- evidently forms on mixing DMSO and SO_3/pyridine, and upon addition of the alcohol and triethylamine this forms the ROS^+Me_2 species common to most DMSO oxidations; this alkoxysulfonium ion then reacts with added Et_3N, leading to the carbonyl product. This procedure involves operation near rt, which can be an advantage relative to the use of dimethyl sulfoxide–oxalyl chloride and usually gives fast reactions and good yields with minimal formation of byproducts. Some examples are shown in eqs 1 and 2.[3b,c] Oxidation with DMSO–SO_3/pyridine avoids the side reaction of chlorination of a pyrrole nucleus encountered with DMSO/$(COCl)_2$, but it was found necessary to add the SO_3/pyridine complex as a solid and not as a DMSO solution to the alcohol in DMSO–Et_3N–THF for oxidation to occur.[3d]

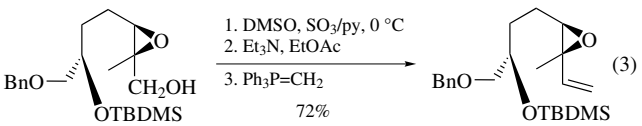


(1)



(2)

In the procedure of eq 3, Et_3N and SO_3/py were added to 0.1 mol of (**1**) at 0 °C, and after stirring the solution was diluted with EtOAc, extracted, and evaporated, and the crude product was dissolved in THF and added to Wittig reagent to give (**2**).[4]



(3)

(1) **(2)**

Related Reagents. *N*-Chlorosuccinimide–Dimethyl Sulfide; Chromic Acid; Dimethyl Sulfide–Chlorine; Dimethyl Sulfoxide–Acetic Anhydride; Dimethyl Sulfoxide–Dicyclohexylcarbodiimide; Dimethyl Sulfoxide–Methanesulfonic Anhydride; Dimethyl Sulfoxide–Oxalyl Chloride; Dimethyl Sulfoxide–Phosphorus Pentoxide; Dimethyl Sulfoxide–Trifluoroacetic Anhydride; Dimethyl Sulfoxide–Triphosgene; Manganese Dioxide; Pyridinium Chlorochromate; Pyridinium Dichromate; Ruthenium(IV) Oxide; Silver(I) Carbonate; 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one.

---

1. (a) Tidwell, T. T., *Org. React.* **1990**, *39*, 297. (b) Tidwell, T. T., *Synthesis* **1990**, 857. (c) Lee, T. V., *Comprehensive Organic Synthesis* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: London, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, 1990. (f) Mancuso, A. J.; Swern, D., *Synthesis* **1981**, 165. (g) Moffatt, J. G. In *Oxidation*; Augustine, R. L.; Trecker, D. J., Eds.; Dekker: New York, 1971; Vol. 2, Chapter 1.

2. (a) Iwai, I.; Ide, J., *Org. Synth., Coll. Vol.* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S., *Org. Synth., Coll. Vol.* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M., *Org. Synth., Coll. Vol.* **1973**, *5*, 755. (d) Varkey, T. E.; Whitfield, G. F.; Swern, D., *J. Org. Chem.* **1974**, *39*, 3365.

3. (a) Parikh, J. R.; Doering, W. v. E., *J. Am. Chem. Soc.* **1967**, *89*, 5505. (b) Schiehser, G. A.; White, J. D., *J. Org. Chem.* **1980**, *45*, 1864. (c) Godfrey, J. D., Jr.; Gordon, E. M.; von Langen, D. J., *Tetrahedron Lett.* **1987**, *28*, 1603. (d) Baker, R.; Castro, J. L., *J. Chem. Soc., Perkin Trans. 1* **1990**, 47.
4. Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K., *J. Am. Chem. Soc.* **1993**, *115*, 3558.

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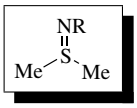
S,S-Dimethyl-*N*-(*p*-toluenesulfonyl)-sulfilimine[1,2]



(**1**; R = *p*-$MeC_6H_4SO_2$)
[13150-75-9] $C_9H_{13}NO_2S_2$ (MW 231.37)
InChI = 1/C9H13NO2S2/c1-8-4-6-9(7-5-8)14(11,12)10-13(2)3/h4-7H,1-3H3
InChIKey = XXOIGDFCELVFFJ-UHFFFAOYAY
(**2**; R = 2,4-$(NO_2)_2C_6H_3$)
[37873-98-6] $C_8H_9N_3O_4S$ (MW 243.27)
InChI = 1/C8H9N3O4S/c1-16(2)9-7-4-3-6(10(12)13)5-8(7)11(14)15/h3-5H,1-2H3
InChIKey = RJNCKRLXEVKKBY-UHFFFAOYAN

(reagents for α-*S,S*-dimethylsulfuranylation of active methylene compounds,[2] and *ortho*-methylation of phenols;[3,4] (**1**) is a methylene transfer agent which converts carbonyl compounds into epoxides[5])

Alternative Name: (**1**) DMTS; (**2**) DMDNS.
Physical Data: (**1**) mp 154–155 °C; (**2**) mp 175–176 °C (dec).
Solubility: insol H_2O; sol ethyl and methyl alcohols, acetone, chloroform, and other common polar organic solvents.
Form Supplied in: (**1**) white solid; (**2**) orange solid.
Preparative Method: (**1**) is conveniently prepared by adding a slight excess of dimethyl sulfide to an aqueous solution of chloramine-T, and collecting the deposited crystals by filtration and recrystallization from ethanol.[1] The yield of white crystalline solid is >95% based on chloramine T.

For preparation of (**2**), phosphorus(V) oxide (60 mmol) is added with stirring to 25 mL of DMF at 0 °C. After 30 min, dimethyl sulfoxide (60 mmol) is added. After stirring for 1 h, 20 mmol of 2,4-dinitroaniline in 25 mL of DMF is added dropwise at 0 °C with continued stirring. After 3 h, 180 mmol of triethylamine is added at 0–5 °C, and stirring is continued for 3 h. The deposited crystals are collected by filtration and recrystallized from THF. The yield of orange crystalline material is 96% based on 2,4-dinitroaniline.[2,3]
Handling, Storage, and Precautions: stable at rt in a sealed bottle, but storage at lower temperature is recommended for (**2**). Use in a fume hood.

Reagent (**2**) reacts with *p*-toluenesulfonamide (at 90 °C for 7 h in DMF) to give (**1**) (58%), in an ylide exchange reaction. Reactions of (**1**) and (**2**) with active methylene compounds in DMF give the corresponding sulfuranes (eq 1). Reagent (**2**), which is more basic than (**1**), gives higher yields of sulfuranes. Furthermore, the yields of the ylide exchange reactions depend on the pK_a value of the active methylene compounds, as shown in Table 1. The lower the pK_a value, the higher the yield of sulfurane.[2,3]

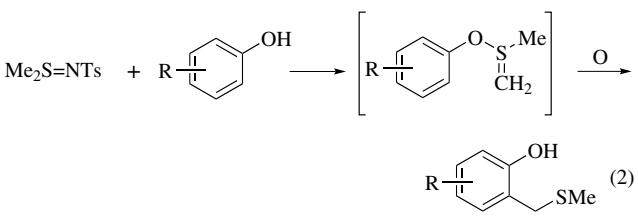
$$Me_2S{=}NR + CH_2R^1R^2 \xrightarrow[90\ °C,\ 7\ h]{DMF} Me_2S{=}CR^1R^2 + H_2NR \quad (1)$$

R = Tos, 2,4-$(NO_2)_2C_6H_3$

Table 1 Results of the reactions of sulfilimines (**1**) and (**2**) with active methylene compounds in DMF at 90 °C for 9 h

	Active methylene compound			
Sulfilimine	R^1	R^2	pK_a	Sulfurane yield (%)
(**2**)	COMe	COMe	8.94	94
(**2**)	COMe	CO_2Et	10.7	80
(**2**)	CN	CN	11.2	98
(**1**)	CN	CN	11.2	12.5
(**2**)	CO_2Me	CO_2Me	–	58
(**2**)	CO_2Et	CO_2Et	13.3	48
(**2**)	Ph	Ph	34.1	0

Reactions of (**1**) and (**2**) with phenols give *o*-methylthiomethylated phenols (eq 2).[3,4] Mixtures of the phenols and 0.5 equiv of (**1**) or (**2**) are heated without solvent at 120–130 °C for 3–7 h. 2-Methylthiomethylphenols are obtained from 2- and 4-methyl, 2,5- and 3,5-dimethyl-, 2,3,5-trimethyl-, and 2-methoxyphenols in 55–95% yield (Table 2). In some case, significant amounts of bis(methylthiomethyl) products are also formed. The yields using (**2**) are higher than those using (**1**).



R = Tos, 2,4-$(NO_2)_2C_6H_3$

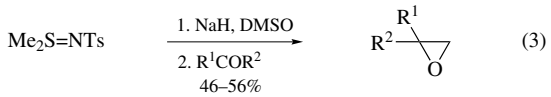
Table 2 Methylthiomethylation of phenols with the sulfilimines (**1**) and (**2**) at 120–130 °C for 3–7 h

Sulfilimine	Phenol	Yield (%)[a]	Sulfilimine	Phenol	Yield (%)[a]
(**2**)	2-MeO	82	(**1**)	2-MeO	78
(**2**)	2-Me	95	(**1**)	2-Me	73
(**2**)	4-Me	55 (24)[b]	(**1**)	2,5-Me_2	96
(**2**)	H	41	(**1**)	3,5-Me_2	58 (35)[b]
(**2**)	4-NO_2	0	(**1**)	2,3,5-Me_3	64

[a] Yields based on reacted sulfilimine.
[b] Data in parentheses show the yields of bis(methylthiomethyl)phenols.

Like *S,S*-dimethyl-*N*-(*p*-toluenesulfonyl)sulfoximine[6] and (dimethylamino)dimethyloxosulfonium tetrafluoroborate,[7] the *N*-tosylsulfilimine (**1**) reacts as a methylene transfer reagent,

converting aldehydes and ketones to epoxides (eq 3). Thus (**1**) is heated at 80–90 °C for 0.5 h in DMSO in the presence of sodium hydride, and the resulting anion is allowed to react with carbonyl compounds to give 1-mono- and 1,1-disubstituted oxiranes in 46–56% yields.[5]



(3)

R^1 = Ph, R^2 = H, Me; R^1R^2 = $(CH_2)_6$

Related Reagents. *N*,*S*-Dimethyl-*S*-phenylsulfoximine; Dimethylsulfonium Methylide; Dimethylsulfoxonium Methylide; *S*,*S*-Dimethyl-*N*-(*p*-toluenesulfonyl)sulfoximine; *S*,*S*-Diphenylsulfilimine.

1. Mann, F. G.; Pope, W. J., *J. Chem. Soc* **1922**, *121*, 1052.
2. Yamamoto, T.; Harigaya, Y.; Okawara, M., *Chem. Lett.* **1972**, 1009.
3. Yamamoto, T.; Harigaya, Y.; Okawara, M., *Tetrahedron* **1978**, *34*, 3097.
4. Yamamoto, T.; Okawara, M., *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2443.
5. Tamura, Y.; Matsushima, H.; Ikeda, M.; Sumoto, K., *Synthesis* **1976**, 35.
6. Johnson, C. R.; Katekar, G. F., *J. Am. Chem. Soc.* **1970**, *92*, 5753.
7. Johnson, C. R.; Rogers, P. E., *J. Org. Chem.* **1973**, *38*, 1793.

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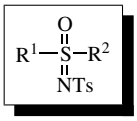
S,S-Dimethyl-*N*-(*p*-toluenesulfonyl)-sulfoximine[1]



(**1**; R^1 = Me, R^2 = Me)
[22236-45-9] $C_9H_{13}NO_3S_2$ (MW 247.37)
InChI = 1/C9H13NO3S2/c1-8-4-6-9(7-5-8)15(12,13)10-14(2,3)11/h4-7H,1-3H3
InChIKey = IRNAWARRPQUZDU-UHFFFAOYAY
(**2**; R^1 = Et, R^2 = Et)
[42153-72-0] $C_{11}H_{17}NO_3S_2$ (MW 275.43)
InChI = 1/C11H17NO3S2/c1-4-16(13,5-2)12-17(14,15)11-8-6-10(3)7-9-11/h6-9H,4-5H2,1-3H3
InChIKey = UCOPCDOTJONZNX-UHFFFAOYAJ
(**3**; R^1 = *i*-Pr, R^2 = *i*-Pr)
[42153-73-1] $C_{13}H_{21}NO_3S_2$ (MW 303.49)
InChI = 1/C13H21NO3S2/c1-10(2)18(15,11(3)4)14-19(16,17)13-8-6-12(5)7-9-13/h6-11H,1-5H3
InChIKey = VHTMFEMNRKXEBH-UHFFFAOYAM
(**4**; R^1 = Ph, R^2 = Me)
[42153-74-2] $C_{14}H_{15}NO_3S_2$ (MW 309.44)
InChI = 1/C14H15NO3S2/c1-12-8-10-14(11-9-12)20(17,18)15-19(2,16)13-6-4-3-5-7-13/h3-11H,1-2H3
InChIKey = JQKZJXZSXOYNRW-UHFFFAOYAN
(**5**; R^1 = Ph, R^2 = *c*-C_5H_9)
[33332-99-9] $C_{18}H_{21}NO_3S_2$ (MW 363.54)
InChI = 1/C18H21NO3S2/c1-15-11-13-18(14-12-15)24(21,22)19-23(20,17-9-5-6-10-17)16-7-3-2-4-8-16/h2-4,7-8,11-14,17H,5-6,9-10H2,1H3
InChIKey = NHGLKWWYXQMWED-UHFFFAOYAE
(**6**; R^1 = Ph, R^2 = Cy)
[33367-88-3] $C_{19}H_{23}NO_3S_2$ (MW 377.57)
InChI = 1/C19H23NO3S2/c1-16-12-14-19(15-13-16)25(22,23)20-24(21,17-8-4-2-5-9-17)18-10-6-3-7-11-18/h2,4-5,8-9,12-15,18H,3,6-7,10-11H2,1H3
InChIKey = WHNOCLRLDBWYOR-UHFFFAOYAX
(**7**; R^1 = Ph, R^2 = Bn)
[38764-59-9] $C_{20}H_{19}NO_3S_2$ (MW 385.54)
InChI = 1/C20H19NO3S2/c1-17-12-14-20(15-13-17)26(23,24)21-25(22,19-10-6-3-7-11-19)16-18-8-4-2-5-9-18/h2-15H,16H2,1H3
InChIKey = LZAYEBHRRACFQN-UHFFFAOYAL

(conversion of aldehydes and ketones to oxiranes,[1,2] ketones or oxiranes to oxetanes,[3] imines to aziridines,[1,2] and electrophilic alkenes to cyclopropanes[1,2])

Alternate Name: *S,S*-dimethyl-*N*-tosylsulfoximine.

Physical Data: (**1**) mp 167–169 °C, 170 °C (from ethanol);[2,4] (**2**) mp 89–91 °C; (**3**) mp 75–77 °C; (**4**) mp 107–109 °C; (**5**) mp 143–144 °C; (**6**) mp 145–146 °C; (**7**) mp 148–149 °C.

Solubility: moderately sol EtOH, THF, DMSO.

Form Supplied in: (**1**) white solid; commercially available.

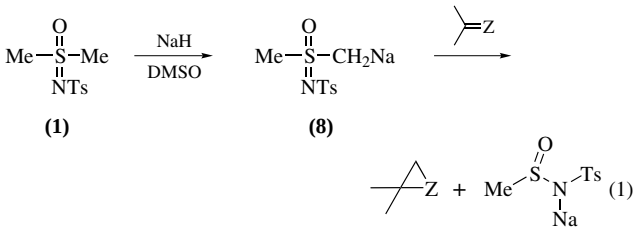
Preparative Methods: excess DMSO containing copper(II) chloride (or another copper catalyst)[2,4] is treated with chloramine-T trihydrate. (**1**) is obtained in 90% yield after aqueous EDTA workup and recrystallization from ethanol.

The other *N*-tosylsulfoximines can be prepared by the tosylation of N–H sulfoximines with *p*-toluenesulfonyl chloride in the presence of base,.[2] but the two most useful and general methods are the oxidation of *N*-tosylsulfilimines with basic hydrogen peroxide,[5] *m*-chloroperbenzoic acid anion,[6] sodium hypochlorite,[8] or ruthenium(VIII) oxide/sodium metaperiodate[7] and the copper powder-promoted reaction of sulfoxides with *p*-toluenesulfonyl azide[2,9]

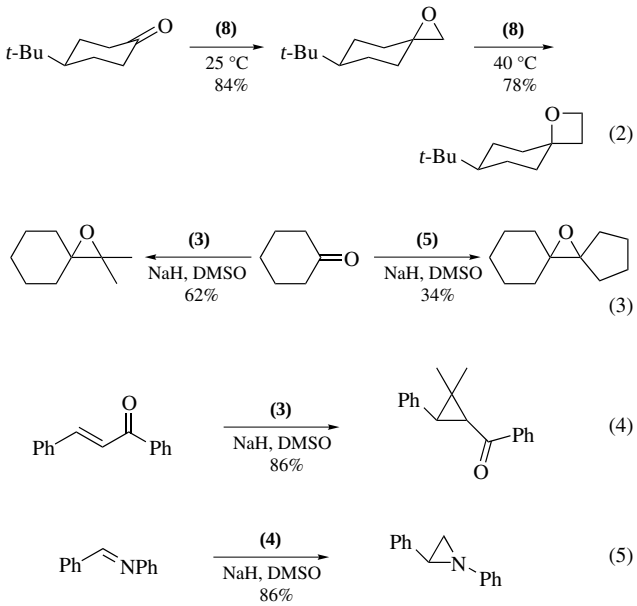
Handling, Storage, and Precautions: (**1**) is a highly crystalline compound with no known toxicity and unlimited shelf life.

The generation of *N*-*p*-toluenesulfonyl-sulfonimidoyl-stabilized carbanions is best accomplished by stirring a slurry of *N*-tosylsulfoximine, e.g. **1**, and sodium hydride in DMSO at rt until hydrogen evolution ceases (2–4 h). THF solutions of the lithium salts of *N*-tosylsulfoximines can be prepared by deprotonation with butyllithium. These anions, which are quite stable at room or slightly elevated temperatures, form a class of nucleophilic alkylidene transfer reagents. The mechanism of these transfer reactions is similar to that of sulfonium ylide reactions but the leaving groups are water-soluble anions rather than neutral molecules (eq 1). The nucleophilic transfer chemistry of sodium *N*-tosylmethanesulfonimidoylmethide **8** is similar to that of dimethylsulfoxonium methylide[10] in regard to regio- and stereochemical selectivity in that the products reflect thermodynamic control.[11] Anion **8** has been reported to be superior to dimethylsulfonium and dimethylsulfoxonium

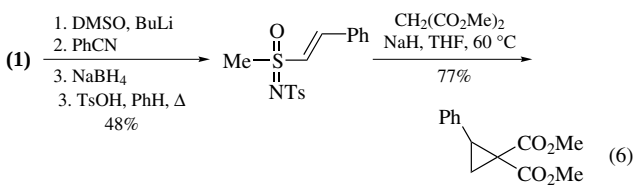
methylides for reactions in which enolate formation is a serious problem.[12]



These salts have been used to prepare oxiranes from aldehydes and ketones (eqs 2 and 3),[2] cyclopropanes from enones (eq 4),[2] and aziridines from imines (eq 5).[2] Alkylidene groups which have been transferred using reagents in this series include methylene, ethylidene, isopropylidene, benzylidene, cyclopentylidene, and cyclohexylidene. Optically active versions of these reagents have been studied, but enantiomeric excesses of the resulting alkylidene transfer products have only been modest.[2] The reaction of carbanion **8** with epoxides results in the expansion of the ring by one carbon (eq 2). This unique oxetane synthesis, which can be carried out in one step by simply treating the ketone with 3 equiv of **8**, is quite general and illustrates the use of **1** as a [$^{-}CH_2CH_2^{+}$] synthon.[3]



Reagent **1** can also be converted to an ethylene transfer reagent by condensation with benzonitrile, followed by reduction of the ketosulfoximine and dehydration (eq 6). The resulting *S*-vinyl-*N*-tosylsulfoximine reacts with stabilized anions to give cyclopropanes.[13] The *N*-tosyl group in *N*-tosylsulfoximines can be cleaved reductively using sodium anthracenide.[14]



Related Reagents. *N*,*S*-Dimethyl-*S*-phenylsulfoximine; Dimethylsulfonium Methylide; Dimethylsulfoxonium Methylide; Diphenylsulfonium Methylide; Isopropyldiphenylsulfonium Tetrafluoroborate.

1. (a) Johnson, C. R., *Aldrichim. Acta* **1985**, *18*, 3. See also: (b) Kennewell, P. D.; Taylor, J. B., *Chem. Soc. Rev.* **1980**, *9*, 477; (c) Oae, S.; Furukawa, N. In *Sulfilimines and Related Derivatives*; American Chemical Society: Washington, 1983.
2. Johnson, C. R.; Krichhoff, R. A.; Reischer, R. J.; Katekar, G. F., *J. Am. Chem. Soc.* **1973**, *95*, 4287.
3. Welch, S. C.; Rao, A. S. C. P.; Lyon, J. T.; Assercq, J.-M., *J. Am. Chem. Soc.* **1983**, *105*, 252.
4. (a) Carr, D.; Seden, T. P.; Turner, R. W., *Tetrahedron Lett.* **1969**, 477; (b) Heintzelman, R. W.; Swern, D., *Synthesis* **1976**, 731.
5. Johnson, C. R.; Krichhoff, R. A., *J. Org. Chem.* **1979**, *44*, 2280.
6. Huang, S.-L.; Swern, D., *J. Org. Chem.* **1979**, *44*, 2510.
7. (a) Veale, H. S.; Levin, J.; Swern, D., *Tetrahedron Lett.* **1978**, 503. (b) Ketcha, D. M.; Swern, D., *Synth. Commun.* **1984**, *14*, 915.
8. Akutagawa, K.; Furukawa, N.; Oae, S., *J. Org. Chem.* **1984**, *49*, 2282.
9. Kwart, H.; Kahn, A. A., *J. Am. Chem. Soc.* **1967**, *89*, 1950.
10. Corey, E. J.; Chaykovsky, M., *J. Am. Chem. Soc.* **1965**, *87*, 1353.
11. Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R., *J. Am. Chem. Soc.* **1973**, *95*, 7424.
12. Andersen, N. H.; Ladner, D. W.; Moore, A. L., *Synth. Commun.* **1978**, *8*, 437.
13. Johnson, C. R.; Lockard, J. P.; Kennedy, E. R., *J. Org. Chem.* **1980**, *45*, 264.
14. Johnson, C. R.; Lavergne, O., *J. Org. Chem.* **1989**, *54*, 986.

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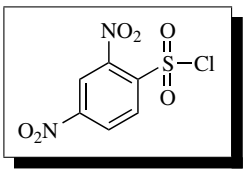
2,4-Dinitrobenzenesulfonyl Chloride



[1656-44-6] $C_6H_3ClN_2O_6S$ (MW 266.62)

InChI = 1/C6H3ClN2O6S/c7-16(14,15)6-2-1-4(8(10)11)3-5(6)9(12)13/h1-3H

InChIKey = SSFSNKZUKDBPIT-UHFFFAOYAY

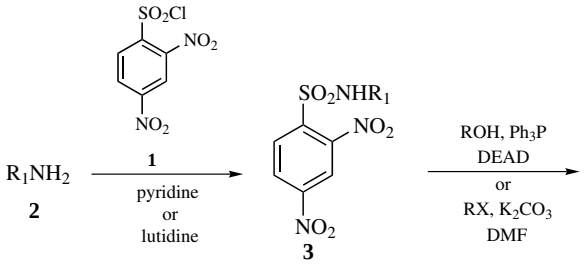
(reagent widely used as a temporary protecting group for amines[1])

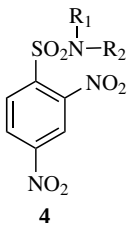
Alternate Names: 2,4-dinitrophenylsulfonyl chloride, dNBS.
Physical Data: mp 102 °C; fp 206.6 ± 46.7 °C.
Solubility: soluble in most organic solvents.
Form Supplied in: white solid, widely available.
Stability: stable under normal temperatures and pressures.
Preparative Methods: by chlorination of a dilute aqueous solution of freshly prepared 2,4-dinitrophenyl isothiourea

hydrochloride.[2] In 55–60% yield by interaction of $ClSO_3H$ and sodium 2,4-dinitrosulfonate (obtained from 2,4-$(O_2N)_2C_6H_3Cl$ and Na_2SO_3).[3]

Handling, Storage, and Precautions: handle with care, potentially toxic. Use only in a well ventilated area. Store in a tightly closed container.

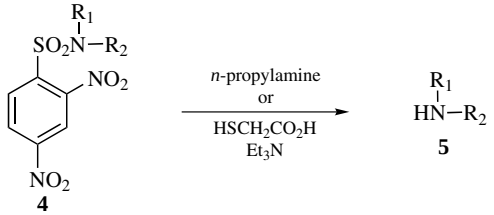
Synthesis of 2,4-Dinitrobenzenesulfonamides (Dns) and *N,N*-Disubstituted 2,4-Dinitrophenylsulfonamides. *N*-Monosubstituted 2,4-dinitrophenylsulfonamides (**3**) are readily prepared from 2,4-dinitrophenylsulfonyl chloride (**1**) and the corresponding primary amines (**2**). The reaction of *N*-monosubstituted 2,4-dinitrophenylsulfonamides (**3**) under Mitsunobu conditions (ROH, DEAD, Ph_3P, benzene) or under conventional conditions (RX, K_2CO_3, DMF) gives *N,N*-disubstituted 2,4-dinitrophenylsulfonamides (**4**), in excellent yields (eq 1). The preferential use of dinitrobenzenesulfonamides, as compared to mononitrobenzenesulfonamides, can be rationalized by a higher rate of sulfonamide formation and, in particular, a higher rate of the subsequent Mitsunobu reaction, due to the lower p*K*a value of the amide proton.[4]



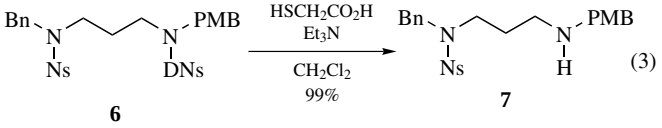


(1)

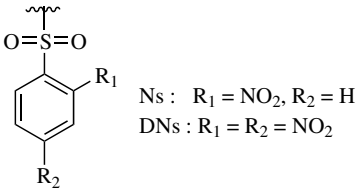
Deprotection of 2,4-Dinitrobenzenesulfonamides. Facile deprotection of sulfonamides (**4**) can be achieved by treatment with excess *n*-propylamine or $HSCH_2CO_2H$ and Et_3N to give the desired secondary amines (**5**) in quantitative yields (eq 2). The latter procedure is more convenient in that the by-product, 2,4-dinitrophenylthioacetic acid, can be easily removed by washing the etherial layer with an aq $NaHCO_3$ solution. This deprotection method was advantageously used in selective deprotection of 2,4-dinitrophenylsulfonamides in the presence of a nitrophenylsulfonamide group in the synthesis of polyamines (eq 3).[1]



(2)

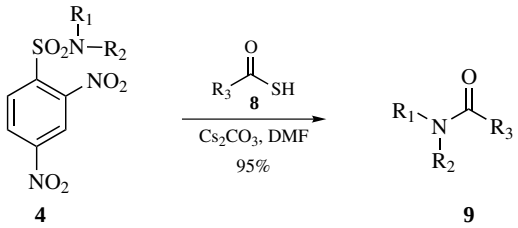


(3)



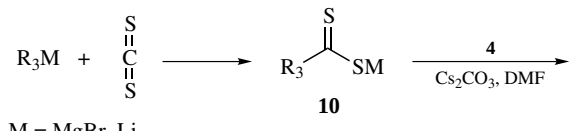
Synthesis of Amines, Amides, Ureas, Thioamides, and Thioureas. The Fukuyama-Mitsunobu reaction is the best method to synthesize secondary amines from primary amines, avoiding formation of undesired tertiary amines and/or the quaternary ammonium salts (eq 1).[4]

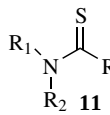
Tomkinson employed the 2,4-dinitrophenylsulfonamide group in a novel deprotection/functionalization sequence for the one-pot preparation of amides, ureas, thioamides, and thioureas. For example, treatment of *N,N*-disubstituted 2,4-dinitrophenylsulfonamide (**4**) with a thioacid (**8**), and cesium carbonate in DMF led to corresponding amides (**9**) in 95% yield (eq 4).[5]



(4)

The reaction was extended to dithioacids (**10**) and dithiocarbamic acids (**12**), which are prepared in situ from carbon disulfide and organometallic compounds and amines, respectively, yielding thioamides (**11**) (eq 5) and thioureas (**13**) (eq 6).[6] This method provides access to di- and trisubstituted thioureas without having to use the highly toxic thiophosgene, or phosphorous triamides.





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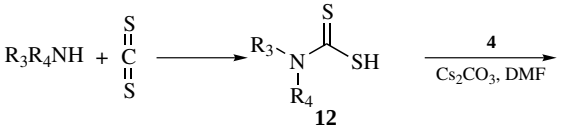
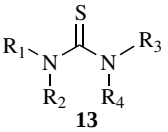
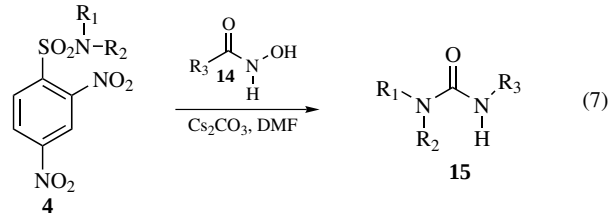




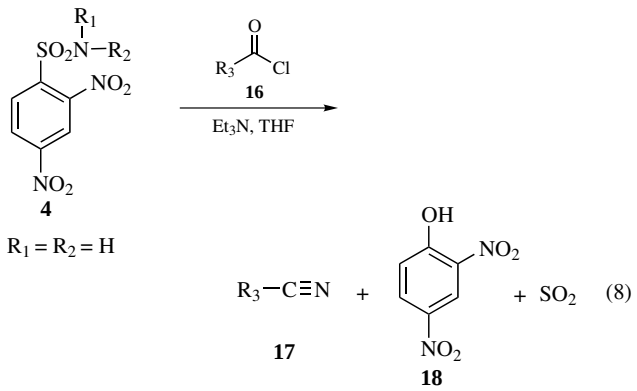
(6)

In a sequence involving a Lossen rearrangement, the treatment of *N*,*N*-disubstituted 2,4-dinitrophenylsulfonamides (**4**) with hydroxamic acid (**14**), and cesium carbonate in DMF led to the corresponding ureas (**15**) in 79% yield (eq 7).[6]



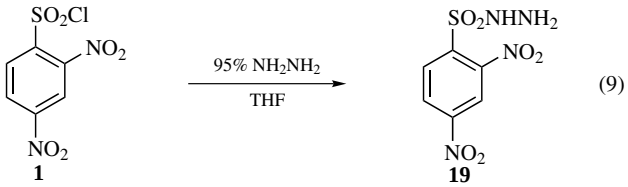
(7)

Synthesis of Nitriles from Acyl Chlorides. Acyl chlorides can be converted into the corresponding nitriles in good yields by reaction of 2,4-dinitrobenzenesulfonamide and triethylamine in THF.[7] Presumably, the reaction with 2,4-dinitrobenzenesulfonamide and acyl chloride involves a Smiles rearrangement[8] to give a nitrile, 2,4-dinitrophenol, and sulfur dioxide (eq 8).



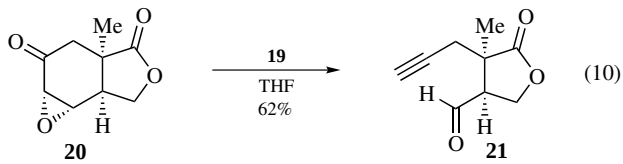
(8)

Synthesis of 2,4-Dinitrobenzenesulfonylhydrazine. Addition of 2,4-dinitrobenzenesulfonyl chloride to a cold, stirred solution of 95% hydrazine in THF, provides 2,4-dinitrobenzenesulfonylhydrazine (**19**) in 70% yield (eq 9).[9]



(9)

2,4-Dinitrobenzenesulfonylhydrazine (**19**) has been found to be a useful reagent in the Eschenmoser cleavage of α,β-epoxy ketones (**20**), especially in instances where the product is an acetylenic aldehyde such as compound **21** (eq 10).[9]



(10)

Related Reagents. 2-Nitrobenzenesulfonyl Chloride; 4-Nitrobenzenesulfonyl Chloride; Nitrobenzenesulfonamide; Benzenesulfonyl Chloride.

1. Kan, T.; Fukuyama, T., *Chem. Commun.* **2004**, 353.
2. Sprague, J. M.; Johnson, T. B., *J. Am. Chem. Soc.* **1937**, *59*, 2439.
3. Lunt, E., *J. App. Chem.* **1957**, *7*, 446.
4. Fukuyama, T.; Cheung, M.; Jow, C. K.; Hidai, Y.; Kan, T., *Tetrahedron Lett.* **1997**, *38*, 5831.
5. Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O., *Tetrahedron Lett.* **1998**, *39*, 1669.
6. Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O., *Tetrahedron Lett.* **1998**, *39*, 1673.
7. Huber, V. J.; Bartsch, R. A., *Tetrahedron* **1998**, *54*, 9281.
8. Warren, L. A.; Smiles, S. J., *J. Chem. Soc.* **1930**, *956*, 1327.
9. Corey, E. J.; Sachdev, H. S., *J. Org. Chem.* **1975**, *40*, 579.

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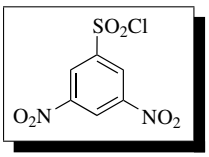
3,5-Dinitrobenzenesulfonyl Chloride



[31206-25-4] $C_6H_3ClN_2O_6S$ (MW 266.63)
InChI = 1/C6H3ClN2O6S/c7-16(14,15)6-2-4(8(10)11)1-5(3-6)9(12)13/h1-3H
InChIKey = GSTCLLCEBJUOLB-UHFFFAOYAA

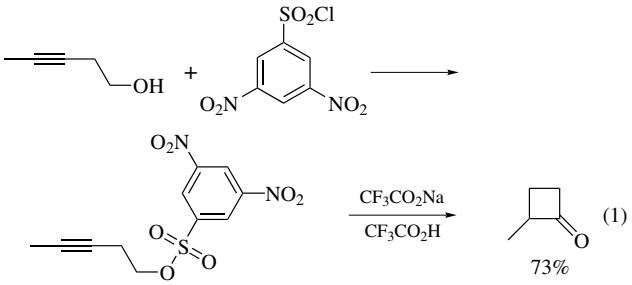
(sulfonylating agent for the preparation of crystalline sulfonamides and sulfonate esters; 3,5-dinitrobenzenesulfonate esters exhibit high reactivity in solvolysis reactions[1,2])

Physical Data: mp 98.5 °C.
Solubility: sol AcOH, pyridine; insol diethyl ether.
Form Supplied in: not commercially available; easily prepared.
Preparative Method: by a modified Sandmeyer reaction.[3,4] Diazotization of 3,5-dinitroaniline (0.25 mol) at −15 °C in aqueous acetic acid/conc HCl followed by addition to a saturated solution of SO_2 in acetic acid gives the product, which is precipitated by the addition of water, washed with water then diethyl ether, and dried under vacuum (81% yield).
Handling, Storage, and Precautions: reactive sulfonylating agent: avoid contact with skin and mucous membranes. Can be stored at rt for prolonged periods when dried and kept free of moisture.

General Reactions. Arenesulfonyl chlorides are vital precursors for the preparation of a wide variety of functional groups including sulfonate esters, sulfonamides, and sulfones. A variety of substituted arenesulfonyl chlorides can be used to derivatize

alcohols and primary and secondary amines forming sulfonate esters and sulfonamides, respectively. Substituted arenesulfonate esters exhibit varying rates of S_N1 and S_N2 reactions which are dependent on the aryl substituents.[2]

Solvolysis of 3,5-Dinitrobenzenesulfonates. Solvolysis of the crystalline 3,5-dinitrobenzenesulfonate of 3-pentyn-1-ol in CF_3CO_2H–CF_3CO_2Na gives 2-methylcyclobutanone[1] in 73% yield (eq 1). The yield of 2-methylcyclobutanone was reduced when the *p*-toluene- and *m*-nitrobenzenesulfonates were used. Cyclobutanone[5] and other alkyl-substituted cyclobutanones[6] have also been prepared via this participation of an alkynic bond during solvolysis of homopropargylic sulfonate esters, but the former requires the use of the more reactive trifluoromethanesulfonate.



Related Reagents. *p*-Anisolesulfonyl Chloride; Benzenesulfonyl Chloride; 4-Bromobenzenesulfonyl Chloride; Methanesulfonyl Chloride; *p*-Toluenesulfonyl Chloride; Trifluoromethanesulfonyl Chloride.

1. (a) Hanack, M.; Herterich, I., Vött, V., *Tetrahedron Lett.* **1967**, 3871. (b) Hanack, M.; Bocher, S.; Herterich, I.; Hummel, K.; Vött, V., *Justus Liebigs Ann. Chem.* **1970**, *733*, 5.
2. Vizgert, R. V.; Savchuk, E. K., *Zh. Obshch. Khim.* **1956**, *26*, 2261 (*Chem. Abstr.* **1957**, *51*, 4984e).
3. Meerwein, H.; Dittmar, G.; Göllner, R.; Hafner, K.; Mensch, F.; Steinfort, O., *Chem. Ber.* **1957**, *90*, 841 (*Chem. Abstr.* **1958**, *52*, 9003e).
4. Hoffman, R. V., *Org. Synth.* **1981**, *60*, 121.
5. Hanack, M.; Dehesch, T.; Hummel, K.; Nierth, A., *Org. Synth.* **1974**, *54*, 84.
6. Hummel, K.; Hanack, M., *Justus Liebigs Ann. Chem.* **1971**, *746*, 211.

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2,4-Dinitrobenzenesulfonylhydrazide

[53777-75-6] $C_6H_6N_4O_6S$ (MW 262.23)

InChI = 1/C6H6N4O6S/c7-8-17(15,16)6-2-1-4(9(11)12)3-5(6)10(13)14/h1-3,8H,7H2

InChIKey = OEIFSMDIUWGNCS-UHFFFAOYAC

(an effective reagent for preparing propargyl ketones and aldehydes via the Eschenmoser fragmentation[2])

Alternate Name: DNSH.

Physical Data: mp 120 °C.

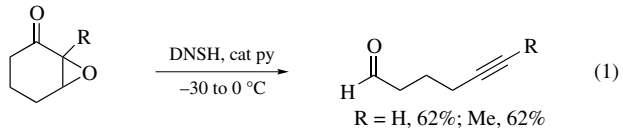
Solubility: sol most organic solvents.

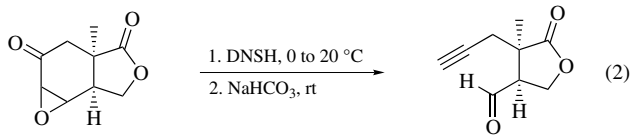
Analysis of Reagent Purity: IR, NMR.

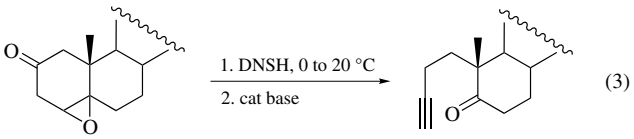
Preparative Method: by treatment of 2,4-dinitrobenzenesulfonyl chloride with 95% hydrazine in THF and crystallized from EtOH/THF.[1]

Handling, Storage, and Precautions: thermally labile; should be stored in a freezer. It is a toxic and potentially flammable solid that should be handled with gloves under inert atmosphere and freshly prepared as needed.

Eschenmoser Fragmentation. Despite reports of the superiority of 2,4-dinitrobenzenesulfonyl hydrazide (DNSH) in the Eschenmoser fragmentation, this reagent has received very little attention as a mild alternative to *p*-toluenesulfonylhydrazide and *N*-aminoaziridines.[2,3] Condensation of DNSH with α,β-epoxy ketones in THF or dichloromethane gives smooth cleavage to alkynones and alkynals between 0 °C and rt (eqs 1–3) when treated with catalytic amounts of base (pyridine, sodium bicarbonate, or sodium carbonate). Yields are good to excellent. The fragmentation shown in eq 2 cannot be effected with *p*-toluenesulfonylhydrazide, and *N*-aminoaziridines give low, irreproducible yields.[1]







Use of this reagent for synthesis of selenosulfonates has also been briefly examined, but mesitylenesulfonylhydrazide is more efficient.[4,5]

1. Corey, E. J., *J. Org. Chem.* **1975**, *40*, 579.
2. Schreiber, J.; Felix, D.; Eschenmoser, M.; Winter, F.; Fautschi, K. H.; Schulte-Elte, E.; Sundt, G.; Ohloff, J.; Kalvoda, J.; Kaufmann, H.; Wieland, P.; Anner, G., *Helv. Chim. Acta* **1967**, *50*, 2101.
3. Felix, D.; Schreiber, J.; Piers, K.; Horn, U.; Eschenmoser, A., *Helv. Chim. Acta* **1970**, *51*, 1461.
4. Back, T. G.; Collins, S., *Tetrahedron Lett.* **1980**, *21*, 2213.
5. Back, T. G.; Collins, S.; Krishna, M. V., *Can. J. Chem.* **1987**, *65*, 38.

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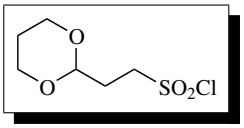
2-(1,3-Dioxan-2-yl)ethylsulfonyl Chloride



[874979-34-7] $C_6H_{11}ClO_4S$ (MW 214.67)

InChI = 1/C6H11ClO4S/c7-12(8,9)5-2-6-10-3-1-4-11-6/h6H,1-5H2

InChIKey = ZNWDPDXGFDWVFA-UHFFFAOYAR

(reagent used as a versatile sulfonating agent for amines; reagent used as protecting and/or activating group of amines)

Alternate Names: 1,3-dioxane-2-ethanesulfonyl chloride; dios-chloride; dios-Cl.

Solubility: sol hexane, ether, CH_2Cl_2, and most organic solvents.

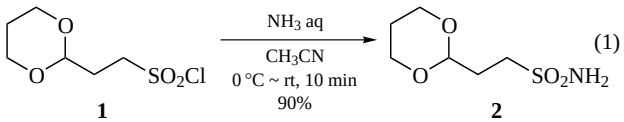
Form Supplied in: not commercially available; colorless liquid.

Preparative Methods: A mixture of 2-(2-chloroethyl)-1,3-dioxane[1] (6.4 mL, 50.6 mmol) and sodium sulfite (7.6 g, 60.1 mmol) was refluxed in DME (100 mL) and water (100 mL) for 3 days. The resulting mixture was concentrated in vacuo, and then the residue was dried over P_2O_5 under reduced pressure (100 °C, 5 mm) for 48 h. This crude product, sodium 2-(1,3-dioxan-2-yl)ethylsulfonate, was suspended in CH_2Cl_2 (150 mL), and then a mixture (0 °C, after 30 min) of triphenylphosphine (26.0 g, 99.2 mmol) and sulfuryl chloride (9.0 mL, 112.0 mmol) in CH_2Cl_2 (150 mL) was added dropwise to the suspension at 0 °C under an argon atmosphere. The resulting mixture was stirred at 0 °C for 2 h, then carefully poured into water (500 mL) and hexane (500 mL) at 0 °C. The organic layer was washed with water (3 × 500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in hexane (250 mL), and the insoluble materials were filtered off. The filtrate was concentrated in vacuo, and the crude product was purified by elution through a short silica gel column chromatography (eluent: ether/petroleum ether, 1/1, v/v) to yield Dios-chloride as a colorless oil (9.02 g, 42.0 mmol, 83%).

Analysis of Reagent Purity: ^{1}H NMR, ^{13}C NMR.

Handling, Storage, and Precautions: corrosive and cytotoxic; handle with care. Stable in a dry atmosphere, but decomposes in protic solvents such as methanol and water with the generation of HCl. Store in a sealed container under nitrogen or argon atmosphere and refrigerate (at −15 °C) for long periods.

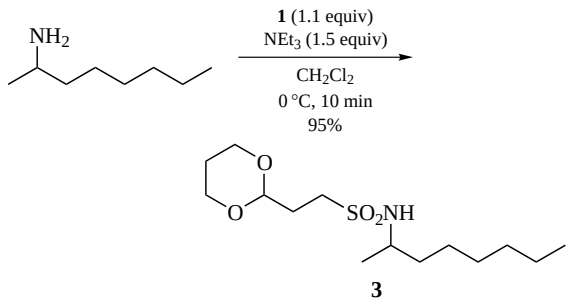
Sulfonation of Amines and Cleavage. The reaction of Dios-Cl (**1**)[2] with ammonia affords water-soluble primary Dios-amide (**2**) in 90% yield (eq 1). Primary (eq 2) and secondary amines (eq 3) are also sulfonated efficiently.



(1)

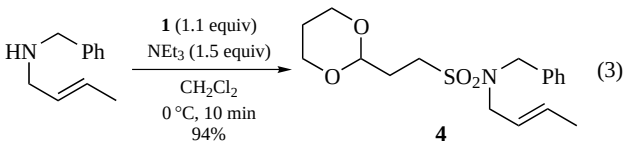
1 **2**

Dios group is highly stable unless the cyclic acetal is hydrolyzed. For example, *N*,*N*-disubstituted (tertiary) Dios-amide (e.g. **4**) is inert under several conditions, such as (1) 2 M KOH, 95 °C in a sealed tube, 12 h, (2) LAH, rt, 12 h, (3) *n*-BuLi, −78 °C ~ rt, 12 h, (4) EtMgBr, −78 °C ~ rt, 12 h. The stability of Dios group is similar to that of 1,3-dioxanes that is well known and well established. Since the Dios group is more stable than a Boc group in acidic conditions, the treatment (TFA/H_2O = 4/1) of (**5**) at 0 °C achieves selective deprotection of the Boc group to give (**6**) in high yield (eq 4).



(2)

3



(3)

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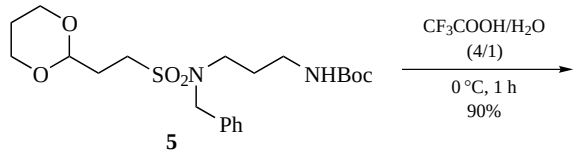

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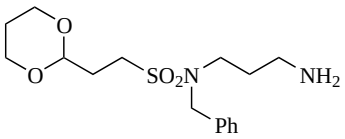
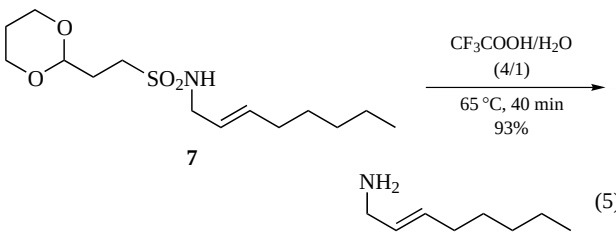


(4)

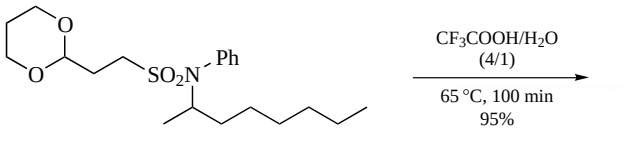
6

Deprotection of secondary (**7**) (eq 5) and tertiary Dios-amides (**8**) (eq 6) is achieved by acid-catalyzed hydrolysis of the acetal moiety to aldehyde in a hot aqueous solution of TFA followed by spontaneous retro-Michael reaction, giving the corresponding primary and secondary amines in excellent yields. Secondary Dios-amide (**7**) can be cleaved more easily than tertiary Dios-amide (**8**). A plausible reaction pathway is shown in eq 7. Acrolein generated as a co-product is not troublesome under these aqueous conditions.



(5)

7



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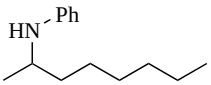

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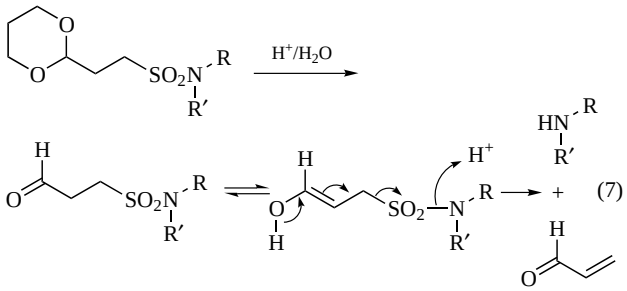
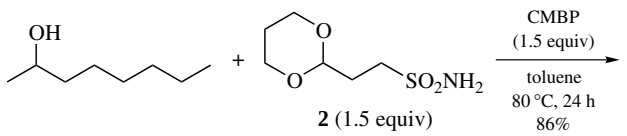
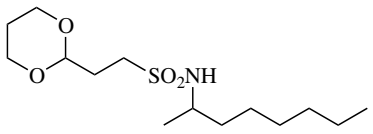


(7)

Activation of Amino Group for Alkylation. The pK_a of primary and secondary Dios-amides (e.g. **3**), an aliphatic sulfonamide, can be estimated to be the same as that of methanesulfonamides (e.g. MsNHMe: pK_a = 11.8).[3] This suggests that the Mitsunobu alkylation of Dios-amides cannot be expected to proceed in high yield when using the original reagent, **DEAD-PPh$_3$**[4,5] However, the use of new Mitsunobu reagent, (cyanomethylene)tributylphosphorane (CMBP),[6–8] promotes the desired Mitsunobu alkylation significantly. For example, the Mitsunobu alkylation of (**2**) proceeded in satisfactory yields to give mono-alkylated amide even with secondary alcohol (eqs 8 and 9). However, allylic (benzylic) alcohol gives over-reacted product (**9**) (double alkylation products) to some extent, because of their high reactivity (eq 10).

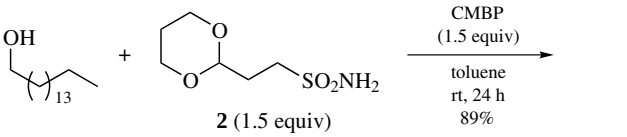


2 (1.5 equiv)

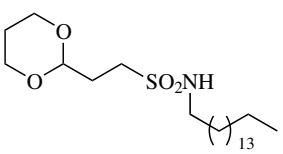


(8)

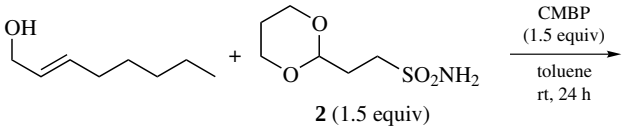
3



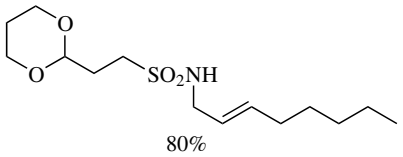
2 (1.5 equiv)



(9)

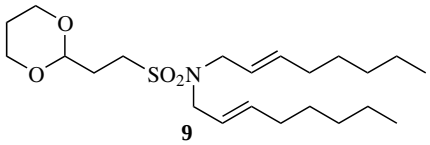


2 (1.5 equiv)



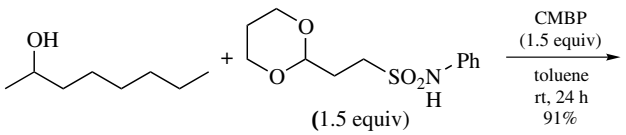
80%

(10)

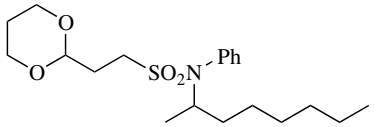


9
19%

Secondary Dios-amides can also be subjected to the Mitsunobu alkylation utilizing CMBP. Although the reaction can be expected to be promoted with satisfactory results by cyanomethylenetrimethylphosphorane (CMMP),[9,10] which is a more highly reactive Mitsunobu reagent than CMBP, the commercially available CMBP possesses sufficient reactivity to afford tertiary Dios-amide in excellent yield (eq 11).

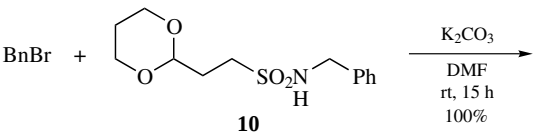


(1.5 equiv)

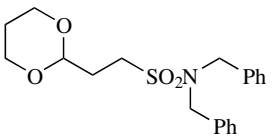


(11)

The alkylation of secondary Dios-amide (e.g. **10**) is also accomplished using alkyl halide under basic conditions (K_2CO_3, DMF, rt, 15 h) to give tertiary Dios-amide in quantitative yield (eq 12). However, the reaction of 2-bromooctane with (**10**) gives poor results owing to competitive elimination (NaH, DMF or THF, 0 °C ~ rt).



10



(12)

1. Gil, G., *Tetrahedron Lett.* **1984**, *25*, 3805.
2. Sakamoto, I.; Izumi, N.; Yamada, T.; Tsunoda, T., *Org. Lett.* **2006**, *8*, 71.
3. King, J. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D. F., *J. Am. Chem. Soc.* **1992**, *114*, 3028.
4. Mitsunobu, O., *Synthesis* **1981**, 1.
5. Hughes, D. L., *Organic React.* **1992**, *42*, 335.

6. Tsunoda, T.; Ozaki, F.; Itô, S., *Tetrahedron Lett.* **1994**, *35*, 5081.
7. Sakamoto, I.; Nishii, T.; Ozaki, F.; Kaku, H.; Tanaka, M.; Tsunoda, T., *Chem. Pharm. Bull.* **2005**, *53*, 1508.
8. Tsunoda, T.; Yamamoto, H.; Goda, K.; Itô, S., *Tetrahedron Lett.* **1996**, *37*, 2457.
9. Tsunoda, T.; Nagino, C.; Oguri, M.; Itô, S., *Tetrahedron Lett.* **1996**, *37*, 2459.
10. Sakamoto, I.; Kaku, H.; Tsunoda, T., *Chem. Pharm. Bull.* **2003**, *51*, 474.

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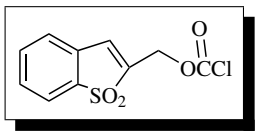
1,1-Dioxobenzo[*b*]-thiophene-2-yl Methyloxycarbonyl Chloride



[135204-19-2] $C_{10}H_7ClO_4S$ (MW 258.68)
InChI = 1/C10H7ClO4S/c11-10(12)15-6-8-5-7-3-1-2-4-9(7)16(8,13)14/h1-5H,6H2
InChIKey = ZYXGPSYADVTJGF-UHFFFAOYAL

(reagent for amino group protection[1])

Alternate Name: benzo[b]thiophenesulfone-2-methyloxycarbonyl chloride, benzo[b]thiophenesulfone-2-methyl chloroformate, Bsmoc-Cl.

Physical Data: mp 76–77 °C.[2]

Solubility: soluble in all common organic solvents.

Analysis of Reagent Purity: ^{1}H NMR, elemental analysis.

Preparative Methods: the title reagent can be prepared from benzenethiophenesulfone-2-methanol by treatment with phosgene in THF.[2]

Handling, Storage, and Precaution: stable in the absence of moisture, unstable toward hydrolysis on TLC plates (silica gel).

Reagent for Amino Group Protection. The Bsmoc group was recommended for protection of the α-amino function of amino acids.[1,2] Such Bsmoc amino acids are useful substitutes for Fmoc amino acids for solid phase and especially rapid continuous solution syntheses of peptides. Deblocking by lower concentrations of piperidine than required for the Fmoc residue avoids base-induced side reactions. An example involves the assembly of pentapeptide **1**.[2]

H-Val-Lys-Asp-Gly-Tyr-Ile-OH

1

An example of Bsmoc-directed rapid solution synthesis involves the assembly of octapeptide **2**.[2]

pGlu-Leu-Thr-Phe-Thr-Pro-Asn-Trp-NH_2

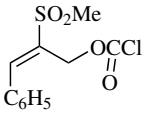
2

Selectivity in Deblocking Relative to Fm-based Protection. Due to the mechanistically distinct deblocking methodology of the Bsmoc residue (Michael-like addition) relative to that of Fmoc-based protecting groups (β-elimination), selectivity in deblocking can be achieved which represents another advantage of Bsmoc utility. Thus dipeptide **3** is exclusively Bsmoc-deblocked by means of 2% tris(2-aminoethyl)amine/dichloromethane and exclusively Fm-deblocked by means of *N*-methylcyclohexylamine or diisopropylamine in dichloromethane.[2]

Bsmoc-Leu-Leu-OFm

3

Related Reagents. 9-Fluorenylmethyl Chloroformate; 2-Methylsulfonyl-3-phenyl-1-prop-2-enyloxycarbonyl Chloride.[3]



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1. Carpino, L. A.; Philbin, M.; Ismail, M.; Truran, G. A.; Mansour, E. M. E.; Iguchi, S.; Ionescu, D.; El-Faham, A.; Riemer, C.; Warrass, R.; Weiss, M. S., *J. Am. Chem. Soc.* **1997**, *119*, 9915.
2. Carpino, L. A.; Ismail, M.; Truran, G. A.; Mansour, E. M. E.; Iguchi, S.; Ionescu, D.; El-Faham, A.; Riemer, C.; Warrass, R. J., *Org. Chem.* **1999**, *64*, 4324.
3. Carpino, L. A.; Mansour, E. M. E., *J. Org. Chem.* **1999**, *64*, 8399.

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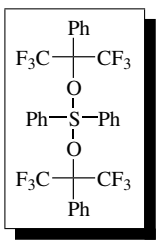
University of Massachusetts, Amherst, MA, USA

Diphenylbis(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxy)sulfurane[1]

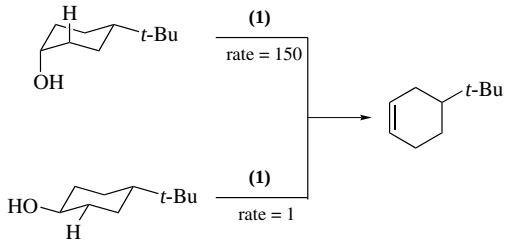


[32133-82-7] $C_{30}H_{20}F_{12}O_2S$ (MW 672.57)
InChI = 1/C30H20F12O2S/c31-27(32,33)25(28(34,35)36,21-13-5-1-6-14-21)43-45(23-17-9-3-10-18-23,24-19-11-4-12-20-24)44-26(29(37,38)39,30(40,41)42)22-15-7-2-8-16-22/h1-20H
InChIKey = RMIBJVUYNZSLSD-UHFFFAOYAX

(dehydration of alcohols;[2] synthesis of epoxides and cyclic ethers;[3] cleavage of amides;[5] oxidation of amines[6])

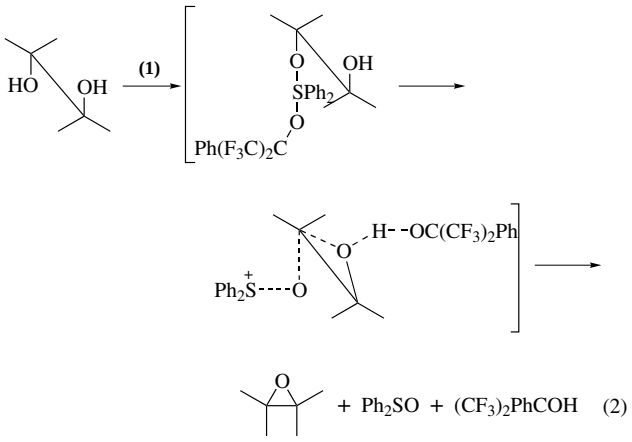
Physical Data: mp 107–109 °C.
Solubility: sol ether, benzene, acetone, alcohols.
Form Supplied in: white crystals.
Analysis of Reagent Purity: NMR, IR.
Preparative Method: by the reaction of the potassium salt of 1,1,1,3,3,3-hexafluoro-2-phenylisopropanol with diphenyl sulfide in the presence of chlorine in ether at −78 °C.[1a]
Handling, Storage, and Precautions: avoid moisture; readily hydrolyzed; stable at rt; decomposes slowly at rt in solution.

Dehydration of Alcohols. The title reagent (**1**) is useful for the dehydration of alcohols. In general, tertiary alcohols are dehydrated instantaneously at rt. Some secondary alcohols are dehydrated. In cyclohexane rings, a *trans*-diaxial orientation of the leaving groups significantly increases the rate of elimination (eq 1). Primary alcohols do not yield products of dehydration unless the β-proton is sufficiently acidic. In most cases, the ether [$(CF_3)_2PhCOR$] is obtained.[2]



(1)

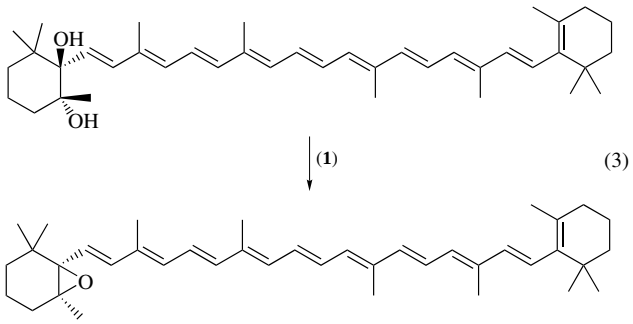
Epoxides. Vicinal diols, capable of attaining an antiperiplanar relationship, can be converted to epoxides (eq 2). The reaction requires 1–2 equiv of (**1**) in chloroform, ether, or carbon tetrachloride and takes place at rt. The reaction is postulated to take place via ligand exchange with the sulfone followed by decomposition to the epoxide, diphenyl sulfoxide, and 1,1,1,3,3,3-hexafluoro-2-phenylisopropanol.



(2)

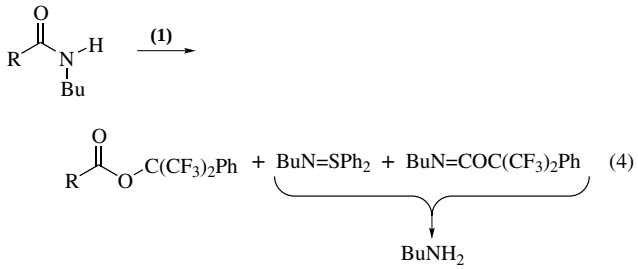
Other cyclic ethers have been prepared, but yields are highly dependent on product ring size. The following transformations are representative: 2,2-dimethyl-1,3-propanediol to 3,3-dimethyloxetane (86%), 1,4-butanediol to tetrahydrofuran (72%), 1,5-pentanediol to tetrahydropyran (39%), and diethylene glycol to dioxane (40%). Longer chain diols yield ethers [$(CF_3)_2PhCO(CH_2)_nOCPh(CF_3)_2$].[3]

Eschenmoser used this method to convert (5*R*,6*R*)-5,6-dihydro-β,β-carotene-5,6-diol to its epoxide (eq 3). This reagent is more effective than other reagents due to the unique solubility profile of the dihydrocarotenediol.[4]



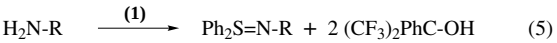
(3)

Cleavage of Amides. Secondary amides can be converted to esters with (**1**). The rate is sensitive to steric constraints at the nitrogen and the acyl carbon. In most cases the amine portion is trapped as the sulfilimine and/or the imidate, which are easily converted back to the amine (eq 4). The dual nature of this reaction affords a mild conversion of amides to esters as well as a simple method for deprotection of *N*-acylated amines.[5]



(4)

Oxidation of Amines. In a related reaction, (**1**) reacts with primary amines (as well as amides and sulfonamides) to give sulfilimines (eq 5). Secondary amines are converted to imines on reaction with (**1**) whereas benzylamine is converted to benzonitrile (89%) with 2 equiv of (**1**).[6]



(5)

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1. (a) *Fieser & Fieser* **1974**, *4*, 205. (b) *Fieser & Fieser* **1975**, *5*, 270. (c) *Fieser & Fieser* **1977**, *6*, 239. (d) *Fieser & Fieser* **1980**, *8*, 208.
2. Martin, J. C.; Arhart, R. J., *J. Am. Chem. Soc.* **1971**, *93*, 4327.
3. Martin, J. C.; Franz, J. A.; Arhart, R. J., *J. Am. Chem. Soc.* **1974**, *96*, 4604.
4. Eschenmoser, W.; Engster, C. H., *Helv. Chim. Acta* **1978**, *61*, 822.
5. (a) Franz, J. A.; Martin, J. C., *J. Am. Chem. Soc.* **1973**, *95*, 2017. (b) Franz, J. A.; Martin, J. C., *J. Am. Chem. Soc.* **1975**, *97*, 6137.
6. Franz, J. A.; Martin, J. C., *J. Am. Chem. Soc.* **1975**, *97*, 583.

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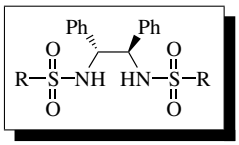
(*R,R*)-1,2-Diphenyl-1,2-diaminoethane *N,N′*-Bis[3,5-bis(trifluoromethyl)-benzenesulfonamide]



(**1**; R = 3,5-$(CF_3)_2C_6H_3$)
[127445-51-6] $C_{30}H_{20}F_{12}N_2O_4S_2$ (MW 764.66)
InChI = 1/C30H20F12N2O4S2/c31-27(32,33)19-11-20(28(34,35)36)14-23(13-19)49(45,46)43-25(17-7-3-1-4-8-17)26(18-9-5-2-6-10-18)44-50(47,48)24-15-21(29(37,38)39)12-22(16-24)30(40,41)42/h1-16,25-26,43-44H/t25-,26-/m1/s1
InChIKey = ZKCACAFCPHDMET-CLJLJLNGBU
(**2**; R = CF_3)
[121788-73-6] $C_{16}H_{14}F_6N_2O_4S_2$ (MW 476.46)
InChI = 1/C16H14F6N2O4S2/c17-15(18,19)29(25,26)23-13(11-7-3-1-4-8-11)14(12-9-5-2-6-10-12)24-30(27,28)16(20,21)22/h1-10,13-14,23-24H/t13-,14-/m1/s1
InChIKey = XQAIGOHPAZPGOU-ZIAGYGMSBU
(**3**; R = 4-MeC_6H_4)
[121758-19-8] $C_{28}H_{28}N_2O_4S_2$ (MW 520.72)
InChI = 1/C28H28N2O4S2/c1-21-13-17-25(18-14-21)35(31,32)29-27(23-9-5-3-6-10-23)28(24-11-7-4-8-12-24)30-36(33,34)26-19-15-22(2)16-20-26/h3-20,27-30H,1-2H3/t27-,28-/m1/s1
InChIKey = SJEDVDWSFHJKIZ-VSGBNLITBB
(**4**; R = 4-$NO_2C_6H_4$)
[121809-00-5] $C_{26}H_{22}N_4O_8S_2$ (MW 582.66)
InChI = 1/C26H22N4O8S2/c31-29(32)21-11-15-23(16-12-21)39(35,36)27-25(19-7-3-1-4-8-19)26(20-9-5-2-6-10-20)28-40(37,38)24-17-13-22(14-18-24)30(33)34/h1-18,25-28H/t25-,26-/m1/s1
InChIKey = MHTMORNTEIWSGV-CLJLJLNGBE

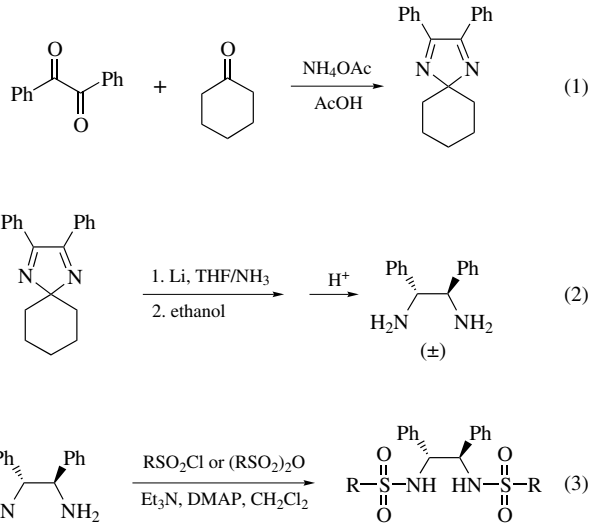
(chiral controller group for enantioselective Diels–Alder reactions,[1] aldol additions,[2] Ireland–Claisen rearrangements,[3] ester-Mannich additions,[4] and carbonyl allylation[5] and propargylation[6])

Alternate Name: (*R,R*)-stilbenediamine *N,N′*-bis-3,5-bis(trifluoromethyl)benzenesulfonamide.

Physical Data: (**1**) mp 155–156 °C; α_D +83.7° (*c* = 1, $CHCl_3$). (**2**) mp 213–214 °C; α_D +6.6° (*c* = 1.4, $CHCl_3$). (**3**) mp 213–214 °C; α_D +43.9° (*c* = 1.74, $CHCl_3$). (**4**) mp 243 °C (dec); α_D 122° (*c* = 0.107, acetone).

Solubility: except for the nitro derivative, the sulfonamides are sol CH_2Cl_2.

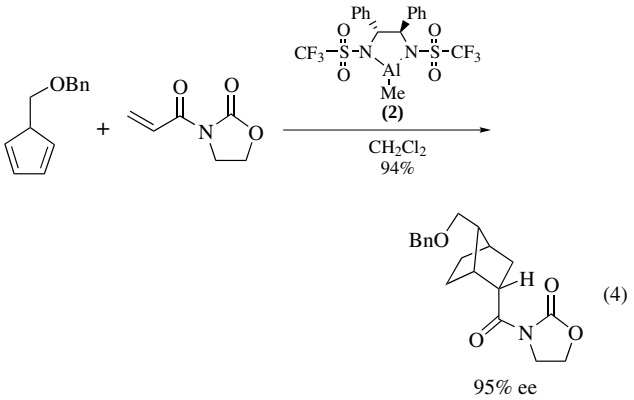
Preparative Methods: the most convenient preparation of (*R,R*)-stilbenediamine is described in *Organic Syntheses*.[7] Condensation of benzil and cyclohexanone in the presence of ammonium acetate and acetic acid (eq 1) produces a spirocyclic 2*H*-imidazole (mp 105–106 °C). Reduction with lithium in THF/NH_3 followed by an ethanol quench and hydrolysis with aqueous HCl (eq 2) affords the racemic diamine as a pale yellow solid (mp 81–82 °C). Resolution is achieved by multiple recrystallizations of the tartaric acid salts from water/ethanol. The sulfonamides are prepared by reaction of the enantiomerically pure diamine with the appropriate anhydride[1b] or sulfonyl chloride[2a] in CH_2Cl_2 in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine (eq 3).



(1) (2) (3)

Handling, Storage, and Precautions: the sulfonamides are all stable, crystalline compounds that do not require any special precautions for storage or handling.

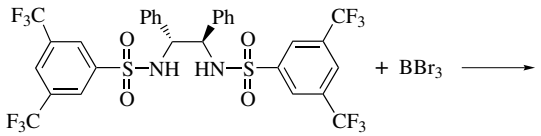
Diels–Alder Reactions. Reaction of the bis(triflamide) (**2**) with diisobutylaluminum hydride or trimethylaluminum affords chiral Lewis acids that catalyze Diels–Alder reactions of acryloyl or crotonoyl derivatives with cyclopentadienes (eq 4).[1] The aluminum complex must be crystallized before use to remove traces of trimethylaluminum. High diastereo- and enantioselectivities are achieved with as little as 0.1 equiv of the Lewis acid, and the chiral sulfonamide is recoverable.



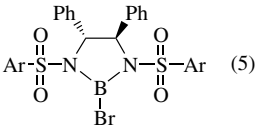
(4)

Asymmetric Aldol Reactions. Reaction of (**1**) with boron tribromide in CH_2Cl_2 affords, after removal of solvent and HBr, a complex (**5**) useful for the preparation of chiral enolates (eq 5).[1a] Complex (**5**) is moisture sensitive and is generally prepared immediately before use. For propionate derivatives, either *syn* or,

less selectively, *anti* aldol adducts may be obtained by selection of the appropriate ester derivative and conditions.[2a] Thus reaction of *t*-butyl propionate with (**5**) and triethylamine produces the corresponding *E*(O) enolate, leading to formation of *anti* aldol adducts upon addition to an aldehyde (eq 6). Selectivities may be enhanced by substitution of the *t*-butyl ester with the (+)-menthyl ester. Conversely, reaction of *S*-phenyl thiopropionate with (**5**) and diisopropylethylamine affords the corresponding *Z*(O) enolates and *syn* aldol products (eq 7).[2a,c]

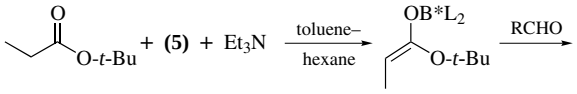


(1)



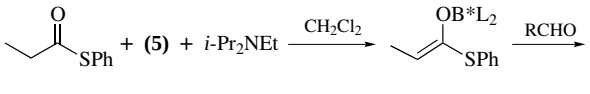
(5)

(5)



R = Ph	93%	98:2 ds	94% ee
R = Cy	82%	94:6 ds	75% ee

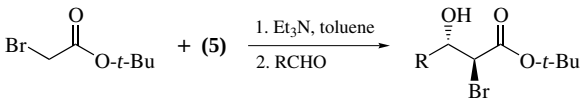
(6)



R = Ph	93%	99:1 ds	97% ee
R = Cy	86%	98:2 ds	91% ee

(7)

Products with low enantiomeric purity are obtained by direct application of this chemistry to unsubstituted acetate esters. However, aldol reactions of *t*-butyl bromoacetate mediated by (**5**) afford synthetically useful bromohydrins (**6**) with high selectivities (eq 8).[2b] These may be reductively dehalogenated or converted to a variety of compounds by way of the derived epoxides.

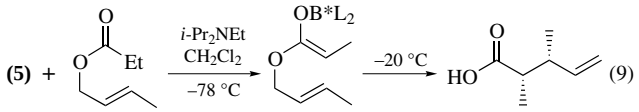


(6)

R = Ph	94%	99:1 ds	98% ee
R = Cy	65%	98:2 ds	91% ee

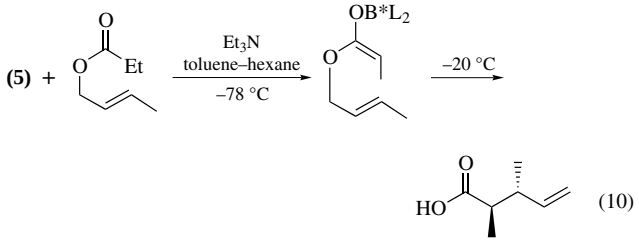
(8)

Asymmetric Ireland–Claisen Rearrangements. Chiral enolates derived from the boron complex (**5**) and allyl esters rearrange with excellent selectivity upon warming to −20 °C for a period of 1–2 weeks (eqs 9 and 10).[3] As discussed above, the geometry of the intermediate enolate can be controlled by appropriate choice of base and solvent, thus allowing access to either *syn* or *anti* configuration in the product. The reaction can be completed in 2–4 days with little erosion in selectivity when run at 4 °C.



75%, 99:1 ds, >97% ee

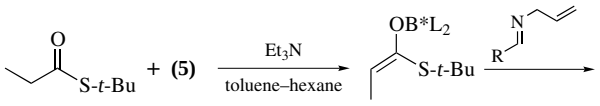
(9)



65%, 90:10 ds, 96% ee

(10)

Ester-Mannich Additions. The *E*(O) enolate (**7**) reacts with *N*-allyl or *N*-benzyl aldimines to afford chiral *β*-amino esters (eq 11).[4] As with the aldol reactions, best selectivities are achieved with imines derived from aromatic or unsaturated aldehydes. The method appears to have good potential for the synthesis of useful *β*-lactams if extended to other enolates.



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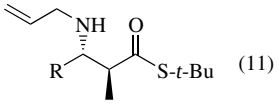
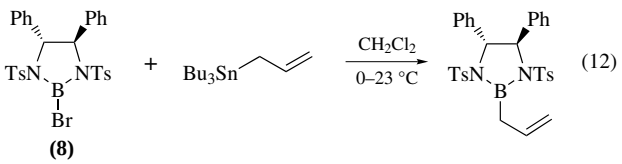


R = Ph	74%	>99:1 ds	90% ee
R = hydrocinnamyl	67%	97:3 ds	70% ee

(11)

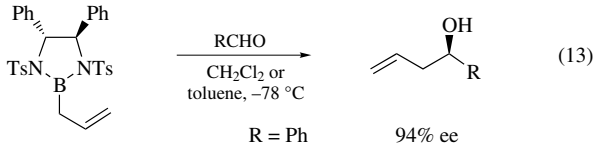
Carbonyl Allylation and Propargylation. Boron complex **8**, derived from the bis(tosylamide) compound (**3**), transmetalates allylstannanes to form allylboranes (eq 12). The allylboranes can be combined without isolation with aldehydes at −78 °C to afford homoallylic alcohols with high enantioselectivity (eq 13).[5] On the basis of a single reported example, reagent control might be expected to overcome substrate control in additions to aldehydes containing an adjacent asymmetric center. The sulfonamide can be recovered by precipitation with diethyl ether during aqueous workup. Ease of preparation and recovery of the chiral controller makes this method one of the more useful available for allylation reactions.



(8)

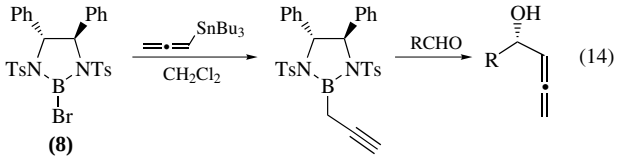
(12)

In the same way, reaction of (**8**) with allenyl- or propargylstannanes affords intermediate borane derivatives which, upon reaction with aldehydes, produce the expected adducts with high selectivities (eqs 14 and 15).[6]

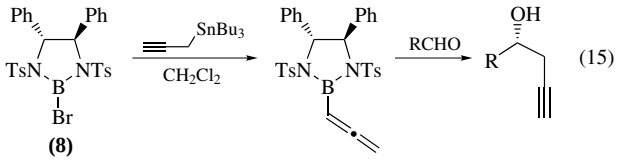


(13)

R = Ph	94% ee
R = cinnamyl	98% ee
R = cyclohexyl	93% ee
R = hexyl	90% ee



(14)



(15)

Other Applications. Other (*R,R*)-stilbenediamine derivatives have been used to direct the stereochemical course of alkene dihydroxylation[8] (with stoichiometric quantities of osmium tetroxide and epoxidation of simple alkenes with sodium hypochlorite and manganese(III) complexes.[9]

Related Reagents. *B*-Allyldiisopinocampheylborane; Chloro-(η^5-cyclopentadienyl)[(*4R,trans*)-2,2-dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2−)-O^{α},O^{α}]titanium; Chloro(cyclopentadienyl)bis[3-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)]titanium; Diisopinocampheylboron Trifluoromethanesulfonate; Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate; (*4R,5R*)-2,2-Dimethyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane–Titanium(IV) Chloride; 2,2-Dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide.

1. (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B., *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Pikul, S.; Corey, E. J., *Org. Synth.* **1992**, *71*, 30.
2. (a) Corey, E. J.; Kim, S. S., *J. Am. Chem. Soc.* **1990**, *112*, 4976. (b) Corey, E. J.; Choi, S., *Tetrahedron Lett.* **1991**, *32*, 2857. (c) Corey, E. J.; Lee, D.-H., *Tetrahedron Lett.* **1993**, *34*, 1737.
3. Corey, E. J.; Lee, D.-H., *J. Am. Chem. Soc.* **1991**, *113*, 4026.
4. Corey, E. J.; Decicco, C. P.; Newbold, R. C., *Tetrahedron Lett.* **1991**, *32*, 5287.
5. Corey, E. J.; Yu, C.-M.; Kim, S. S., *J. Am. Chem. Soc.* **1989**, *111*, 5495.
6. Corey, E. J.; Yu, C.-M.; Lee, D.-H., *J. Am. Chem. Soc.* **1990**, *112*, 878.
7. Pikul, S.; Corey, E. J., *Org. Synth.* **1992**, *71*, 22.
8. Corey, E. J.; DaSilva Jardine, P.; Virgil, S.; Yuen, P.-W.; Connell, R. D., *J. Am. Chem. Soc.* **1989**, *111*, 9243.
9. Zhang, W.; Jacobsen, E. N., *J. Org. Chem.* **1991**, *56*, 2296.

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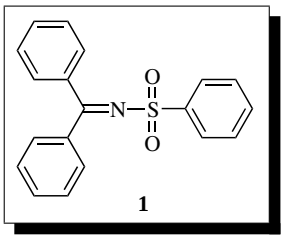
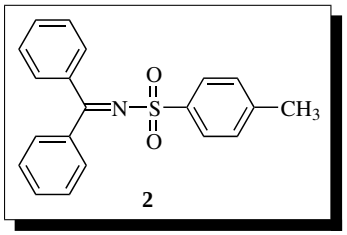
N-(Diphenylmethylene)benzenesulfonamide and *N*-(Diphenylmethylene)-4-methylbenzenesulfonamide



[10398-99-9] $C_{19}H_{15}NO_2S$ (MW 332.42)
InChI = 1/C19H15NO2S/c21-23(22,18-14-8-3-9-15-18)20-19(16-10-4-1-5-11-16)17-12-6-2-7-13-17/h1-15H
InChIKey = LECLPBHPQOFADH-UHFFFAOYAQ

(reagent used as an activated imine)

Physical Data: mp 119–120 °C.
Form Supplied in: colorless crystals. Not commercially available.
Purification: recrystalization from CH_3OH.



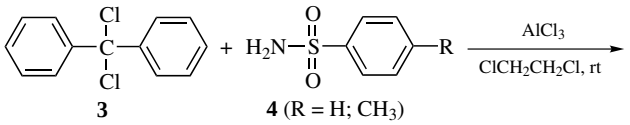
[10399-00-5] $C_{20}H_{17}NO_2S$ (MW 346.45)
InChI = 1/C20H17NO2S/c1-16-12-14-19(15-13-16)24(22,23)21-20(17-8-4-2-5-9-17)18-10-6-3-7-11-18/h2-15H,1H3
InChIKey = ODLFJRFKAOOIKO-UHFFFAOYAB

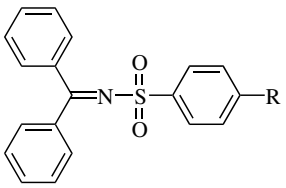
(reagent used as an activated imine)

Physical Data: mp 103–104 °C[1]; 102–103 °C[2]; 101–102 °C[5]; 103 °C[6]; 102–104 °C.[7]
Solubility: soluble in pyridine, dimethylformamide, acetonitrile, dioxane, and tetrahydrofuran.
Form Supplied in: colorless crystals. Not commercially available.
Purification: recrystalization from CH_3OH, from Et_2O–hexane, from EtOAc–hexane, or from benzene.

Preparative Methods. Several methods have been published for the synthesis of *N*-(diphenylmethylene)-4-methylbenzenesulfonamide (**2**), but only two have been applied to the preparation of *N*-(diphenylmethylene)benzenesulfonamide (**1**). Thus, condensation of dichlorodiphenylmethane (**3**) with benzenesulfonamide (**4**, R = H) or 4-methylbenzenesulfonamide (**4**, R = CH_3) in the presence of $AlCl_3$ at room temperature and 1,2-dichloroethane as solvent leads to the corresponding products in high yields[1] (eq 1). Lower yields of products **1** and **2** are obtained when either diphenyldiazomethane (**5**) or benzophenone hydrazone (**6**) condenses with *N*-chloro-*N*-sodiumbenzenesulfonamide (Chloramine-B) (**7**, R = H) or with its 4-methylphenyl derivative

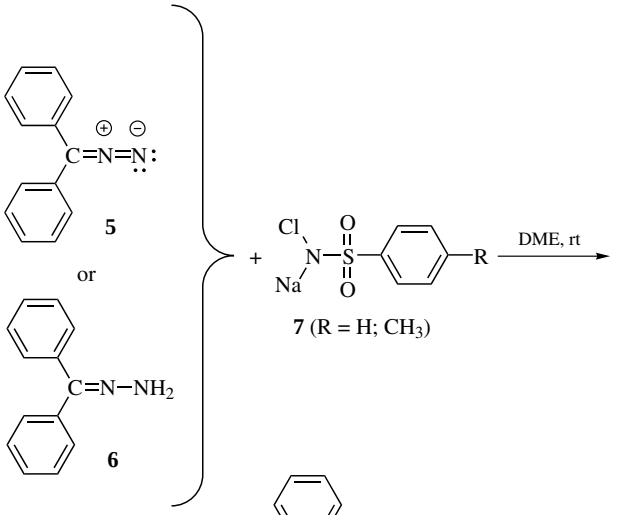
(Chloramine-T) (**7**, R = CH_3) in 1,2-dimethoxyethane (DME) at room temperature (eq 2).[2]

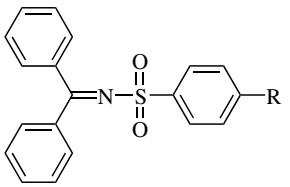




(1)

1, R = H (92%)
2, R = CH_3 (80%)





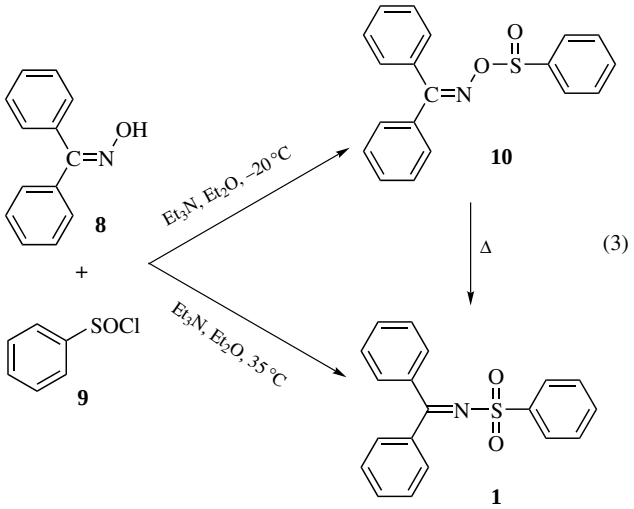
(2)

1, R = H (64%)
2, R = CH_3 (79–82%)

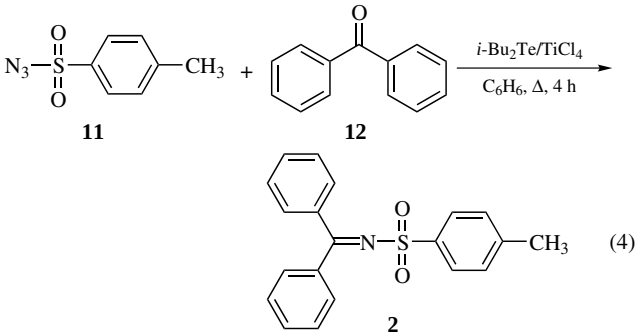
N-(Diphenylmethylene)benzenesulfonamide (**1**) has also been obtained through reaction of benzophenone ketoxime (**8**) with phenylsulphinyl chloride (**9**) in the presence of triethylamine at room temperature. When this reaction is carried out at −20 °C, the *O*-phenylsulphinyl benzophenone oxime (**10**) is formed, which then rearranges to **1** (ca. 85%) when heated (eq 3).[3]

Additionally, the following methodologies have been used in the synthesis of *N*-(diphenylmethylene)-4-methylbenzenesulfonamide (**2**):

1. Coupling reaction of tosyl azide (**11**) with benzophenone (**12**) in a solution of diisobutyl telluride and titanium(IV) chloride in refluxing benzene[4] (eq 4).

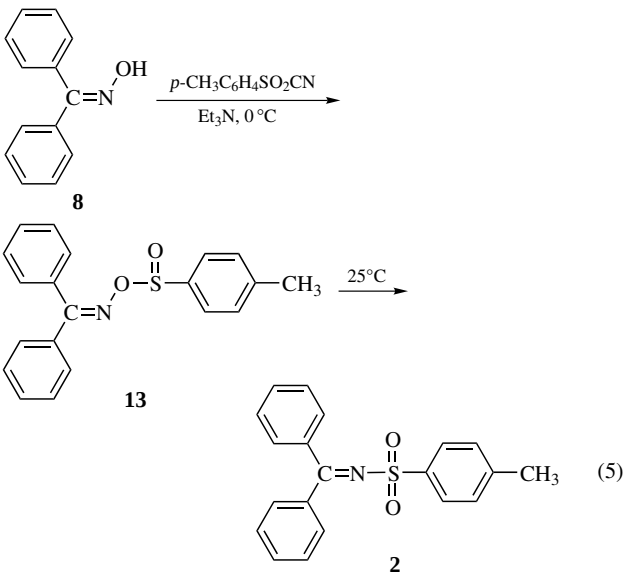


(3)



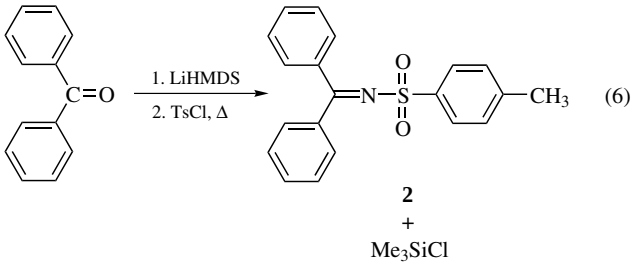
(4)

2. Homolytic rearrangement at room temperature of benzophenone oxime *O*-tosylsulfinate (**13**) prepared from benzophenone oxime (**8**) with tosyl cyanide as reagent (69%)[5] (eq 5).



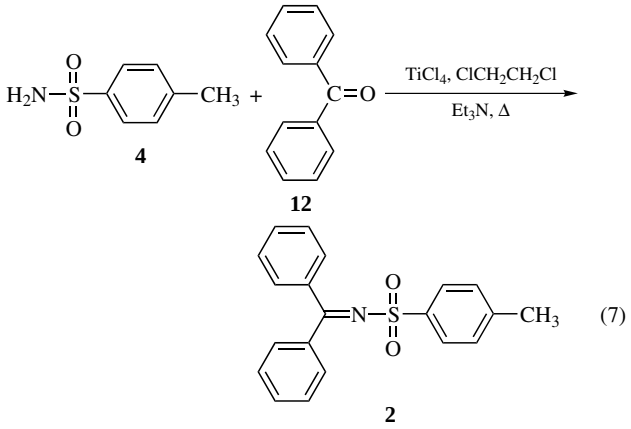
(5)

3. A one-flask, two-step sequence from benzophenone (**12**) via *N*-(trimethylsilyl) benzophenone imine (59% yield) in the presence of *p*-toluenesulfonyl chloride. No purification of the product is necessary as the conversion is quantitative and the by-product, trimethylsilyl chloride is volatile[6] (eq 6).



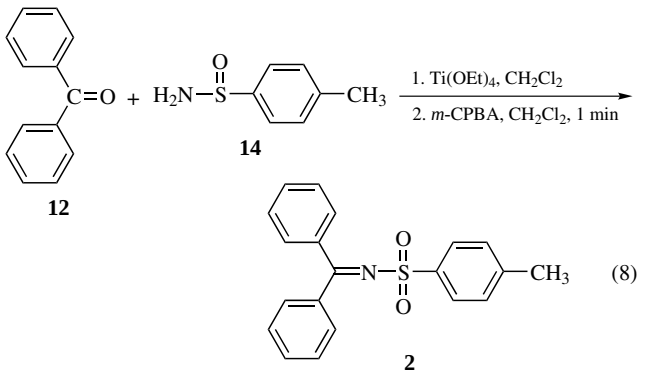
(6)

4. Direct condensation of *p*-toluenesulfonamide (**4**) with benzophenone (**12**) in 1,2-dichloroethane in the presence of $TiCl_4$[7] (eq 7).



(7)

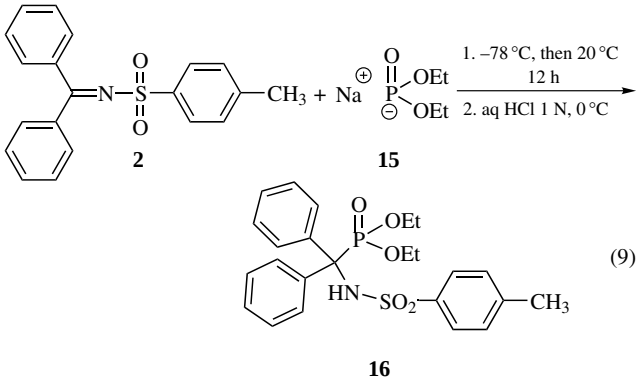
5. In a two-step process consisting of condensation of benzophenone (**12**) with *p*-toluenesulfinamide (**14**) (79%) and further oxidation of the resulting *N*-(*p*-toluensulfinyl)-benzophenone imine with *m*-chloroperbenzoic acid (*m*-CPBA) (88%)[8] (eq 8).



(8)

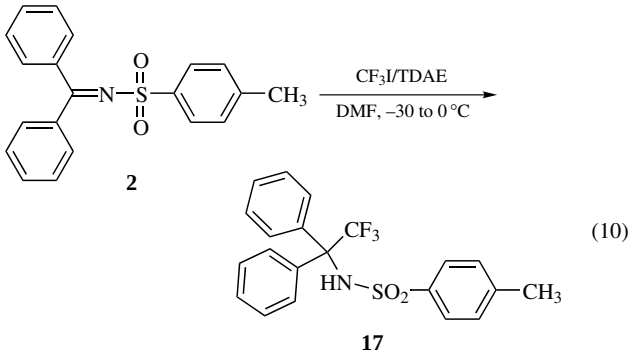
Although *N*-sulfonylimines are useful precursors for the preparation of important synthetic intermediates such as oxaziridines and aziridines, as well as for the synthesis of compounds of biological importance such as *erythro*-α,β-diamino acids, only a handful of reports have been published on the use of *N*-(Diphenylmethylene)-4-methylbenzenesulfonamide (**2**); no reports have appeared for *N*-(Diphenylmethylene)benzenesulfonamide (**1**).

Nucleophilic Addition. Sulfonation of the nitrogen atom of the C=N bond of imines enhances the electrophilicity of the azomethine carbon. Addition of sodium diethylphosphonate (**15**) to *N*-(diphenylmethylene)-4-methylbenzenesulfonamide (**2**) affords *N*-tosyl-α,α-diphenyl(aminomethyl)phosphonate (**16**) (96%), a phosphorylated analog of a $C_{\alpha,\alpha}$-diphenyl amino acid derivative used as proteolytic enzyme inhibitor[9] (eq 9).



(9)

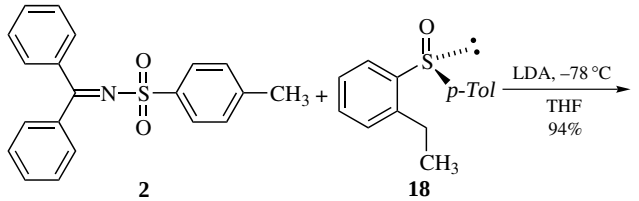
The trifluoromethylation of imines can also be significantly enhanced through *N*-tosylation. *N*-(Diphenylmethylene)-4-methylbenzenesulfonamide (**2**) reacts with the trifluoromethyl anion reagent derived from CF_3I/TDAE (TDAE: tetrakisdimethylamino-ethylene) to afford the adduct (**17**) in 54% yield[10] (eq 10). The *p*-toluenesulfonyl group can be removed from the adduct through treatment with phenol and 48% HBr to give the corresponding trifluoromethylamine.[11]



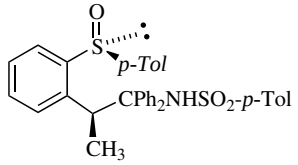
(10)

Although both the symmetrically substituted azomethine carbon and the symmetry of the sulfonyl moiety of *N*-(diphenylmethylene)-4-methylbenzenesulfonamide (**2**) limit its use in asymmetric synthesis, (2*S*)-*N*-{1,1-diphenyl-[(*S*)-3-(*p*-toluenesulfinyl)phenyl]propyl}-*p*-toluenesulfonamide (**19**) has been obtained in almost quantitative yield (94%) and with complete stereoselectivity (de $\geq$ 98%) in the reaction of enantiopure Li carbanion from (*S*)-2-(*p*-toluenesulfinyl)ethylbenzene (**18**) and *N*-(diphenylmethylene)-4-methylbenzenesulfonamide[12] (eq 11), with the *N*-sulfinylimine analog being a factor of 2 less reactive under the same reaction conditions.

Reduction. *N*-(Diphenylmethylene)-4-methylbenzenesulfonamide (**2**) is an electron-deficient aromatic imine that can be reduced to **20** in excellent yield through treatment with 3 equiv of $ZnEt_2$ and 5 mol % of $Ni(acac)_2$ in dioxane[13] (eq 12). Remarkably, this reduction can be achieved in the presence of a ketone.

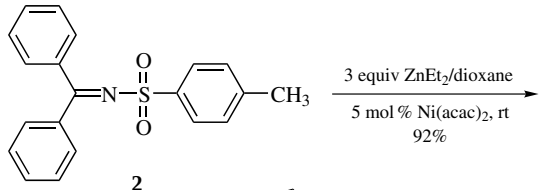


2 **18**



(11)

19 (de ≥98%)



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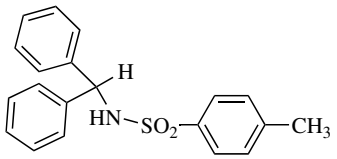
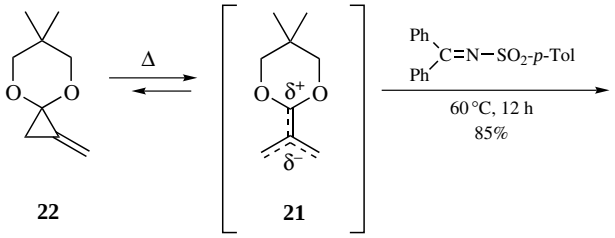


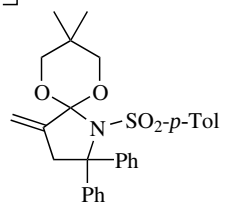
(12)

20

[3 + 2] Cycloaddition. *N*-(Diphenylmethylene)-4-methylbenzenesulfonamide (**2**) has been used as a dienophile in a hetero [3 + 2] cycloaddition. Dipolar trimethylenemethane (TMM, **21**), generated by means of thermolysis of methylenecyclopropane (**22**), undergoes [3 + 2] cycloaddition with the reagent to regioselectively afford the acetal of the α-methylene-γ-lactam product **23**. This product is quite acid-sensitive and may be isolated as the corresponding α-alkylidene-γ-amino ester. The cycloadduct serves as a synthetic precursor to γ-amino acid derivatives[14] (eq 13).



22 **21**



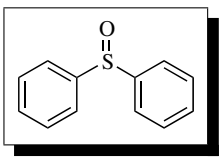
(13)

23

1. Dubina, V. L.; Burmistrov, S. I., *Zh. Org. Khim.* **1967**, *3*, 424. *Chem. Abstract* **1967**, *66*, 115403p.
2. (a) Schoenberg, A.; Singer, E.; Knoefel, W., *Tetrahedron Lett.* **1967**, *19*, 1819. (b) Schoenberg, A.; Singer, E., *Chem. Ber.* **1968**, *101*, 3445.
3. Hudson, R. F.; Record, K. A. F., *J. Chem. Soc., Chem. Commun.* **1976**, 831.
4. Suzuki, H.; Manabe, H.; Enokiya, R.; Hanazaki, Y., *Chem. Lett.* **1986**, 1339.
5. Boger, D. L.; Corbett, W. L., *J. Org. Chem.* **1992**, *57*, 4777.
6. Georg, G. I.; Harriman, G. C. B.; Peterson, S. A., *J. Org. Chem.* **1995**, *60*, 7366.
7. Ram, R. N.; Khan, A. A., *Synth. Commun.* **2001**, *31*, 841.
8. García Ruano, J. L.; Alemán, J.; Cid, M. B.; Parra, A., *Org. Lett.* **2005**, *7*, 179.
9. Cristal, H.-J.; Lambert, J.-M.; Pirat, J.-L., *Synthesis* **1998**, 1167.
10. Xu, W.; Dolbier, W. R., Jr., *J. Org. Chem.* **2005**, *70*, 4741.
11. Prakash, G. K. S.; Mandal, M.; Olah, G., *Synlett* **2001**, 77.
12. García Ruano, J. L.; Alemán, J.; Parra, A., *J. Am. Chem. Soc.* **2005**, *127*, 13048.
13. Xiao, X.; Wang, H.; Huang, Z.; Yang, J.; Bian, X.; Qin, Y., *Org. Lett.* **2006**, *8*, 139.
14. Yamago, S.; Yanagawa, M.; Nakamura, E., *Chem. Lett.* **1999**, 879.

Santos Fustero, Antonio Simón-Fuentes &
Juan F. Sanz-Cervera
Universidad de Valencia, Burjassot, Spain and Centro de Investigación Príncipe Felipe, Valencia, Spain

Diphenyl Sulfoxide



[945-51-7] $C_{12}H_{10}OS$ (MW 202.27)

InChI = 1/C12H10OS/c13-14(11-7-3-1-4-8-11)12-9-5-2-6-10-12/h1-10H

InChIKey = JJHHIJFTHRNPIK-UHFFFAOYAI

(reagent used as an oxidant and hydroxyl activator in combination with a variety of electrophilic reagents)

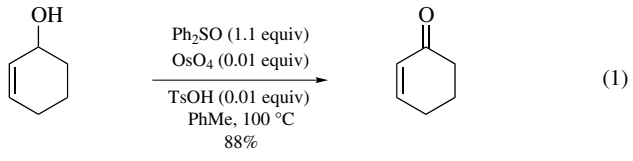
Physical Data: mp 71 °C.
Solubility: soluble in most organic solvents.
Form Supplied in: widely available as white solid.

Original Commentary

David Y. Gin
University of Illinois, Urbana, IL, USA

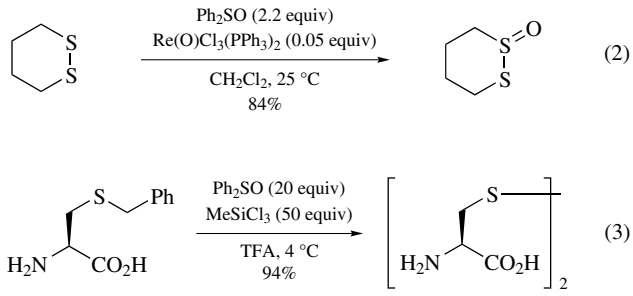
Oxidation of Alcohols. Diphenyl sulfoxide has been employed as an oxidant in conjunction with molybdenum (VI) and osmium (VIII) catalysts for the conversion of alcohols to carbonyl compounds. Diphenyl sulfoxide in combination with catalytic quantities of $MoO_2(acac)_2$ oxidizes alcohols to ketones or aldehydes.[1] Higher yields are obtained with allylic or benzylic alcohols. Catalytic OsO_4 in association with Ph_2SO can oxidize primary and secondary alcohols to aldehydes and ketones in the

presence of catalytic quantities of *p*-toluenesulfonic acid at elevated temperatures (eq 1).[2]



(1)

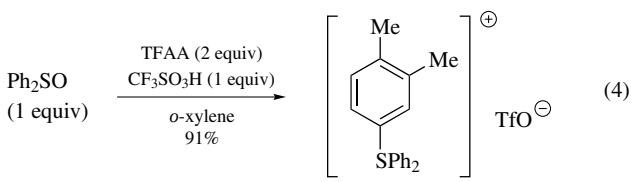
Oxidation of Sulfides and Disulfides. A mild method for the oxidation of dialkyl and monoaryl sulfides to sulfoxides employs $Re(O)Cl_3(PPh_3)_2$ as a catalyst and diphenyl sulfoxide as an oxidant.[3] Over-oxidation to the corresponding sulfone is not observed. The same reagent system can be applied to the efficient oxidation of acyclic symmetrical disulfides to the corresponding thiosulfonates. Cyclic five- and six-membered disulfides afford the corresponding thiosulfinate products with this reagent system (eq 2).[4] The oxidative coupling of *S*-protected cysteine to cystine can be accomplished with Ph_2SO and $MeSiCl_3$ in TFA (eq 3).[5,6] *S*-Protective groups such as acetamidomethyl, benzyl, *p*-methoxybenzyl, *p*-methylbenzyl, and *t*-butyl thioethers are susceptible to the deprotective dimerization process. Other silicon electrophiles, such as TMSCl, $SiCl_4$, and TMSOTf can also be used. This method has been applied to regioselective disulfide formation with complex peptide fragments.[7,8]



(2)

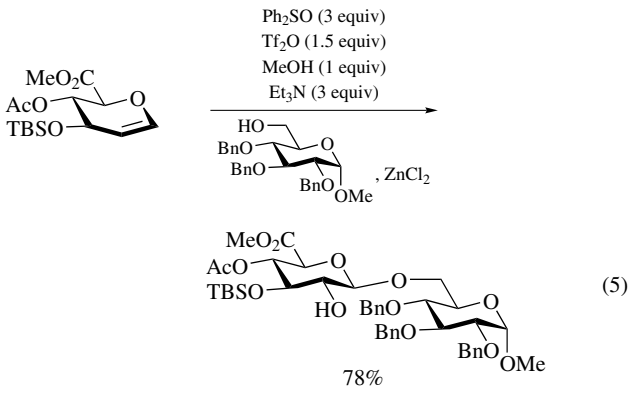
(3)

Electrophilic Aromatic Substitution. When activated with electrophilic reagents, such as trifluoroacetic anhydride (TFAA), diphenyl sulfoxide is converted into an acyloxysulfonium ion, which can effect electrophilic aromatic substitution. When this mode of sulfoxide activation is performed in the presence of simple aromatic substrates, such as *o*-xylene, the corresponding triarylsulfonium salt is formed in good yield (eq 4).[9] The Ph_2SO·TFAA reagent combination reacts similarly with more complex substrates, such as indoles, affording the 3-indolylsulfonium salts.[10]



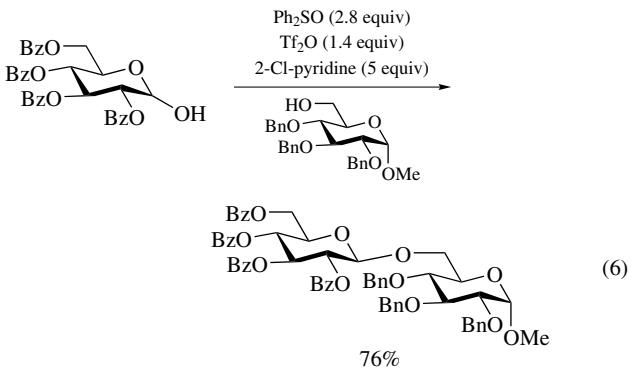
(4)

Oxidative Glycosylation. Glycal substrates undergo rapid electrophilic activation with the reagent combination of Ph_2SO and Tf_2O. In the presence of excess Ph_2SO, transfer of the sulfoxide oxygen to the C_2-position of the glycal occurs. Following the addition of an appropriate nucleophile, C_2-hydroxy glycoside products are obtained (eq 5).[11] This sulfoxide-mediated oxygen transfer reaction was shown to proceed through formation of a 1,2-anhydropyranoside intermediate.[12]



(5)

Dehydrative Glycosylation. The reagent combination of Ph_2SO and Tf_2O is known to rapidly activate the C1-hemiacetal functionality of carbohydrates.[13] Formation of an intermediate glycosyl oxosulfonium species allows for glycosidic bond formation with a wide array of nucleophiles to afford a variety of glycoconjugates (eq 6).[14]



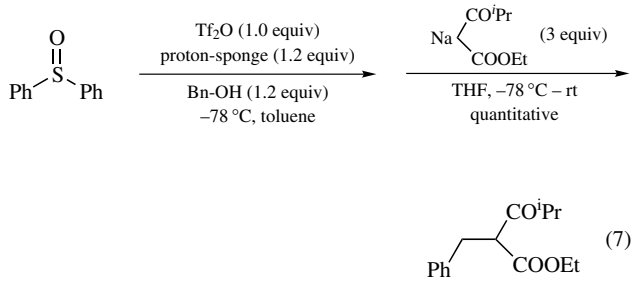
(6)

Other Applications. Mixtures of diphenyl sulfoxide and acid chlorides have been shown to act as chlorinating agents toward alkenes.[15] Diphenyl sulfoxide as well as other dialkyl sulfoxides have also been employed in the solvent extraction separation of various metals.[16]

First Update

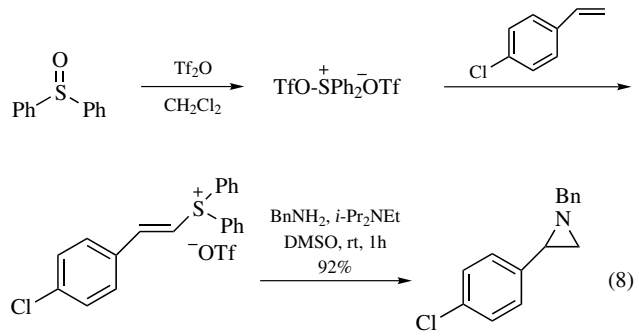
Abhisek Banerjee
University of Illinois at Chicago, Chicago, IL, USA

***C*-Benzylation.** The diphenyl sulfoxide and Tf_2O combination, used in conjunction with benzyl alcohol, can be exploited as an efficient one-pot *C*-benzylating system for various sodium enolates (eq 7).[17]



Predominant formation of the *C*-benzylated product can be understood by considering the soft carbon nucleophile attacking the benzyl carbon of the oxosulfonium trifluoromethane sulfonate, with diphenyl sulfoxide acting as a soft leaving group. The reaction also proceeds smoothly with various other substituted benzyl alcohols with moderate to good yields. Sodium enolates derived from esters, α-cyano esters, α-aromatic and aliphatic ketones can also be benzylated with consistent high yields.

Synthesis of 2-Arylaziridines. An effective and convenient method for the synthesis of 2-arylaziridines from styrene derivatives and primary amines involves the following two-step protocol: preparation of 2-arylethenyl(diphenyl)sulfonium salts from styrenes and the diphenyl sulfoxide-Tf_2O reagent combination at low temperature and subsequent treatment with primary amines (eq 8).[18]

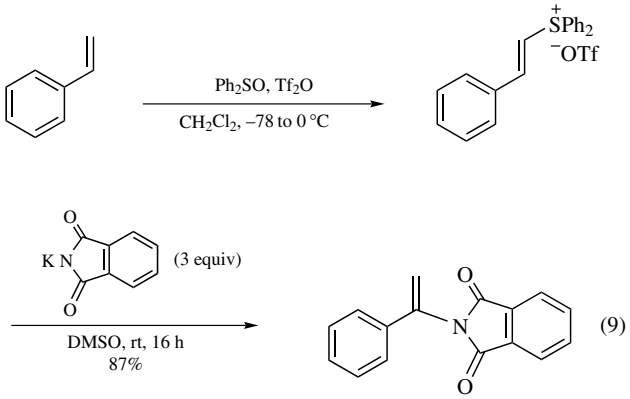


tert-Butylamine can replace Hünig's base in this chemistry and simplifies the work-up procedure because of its low boiling point (46 °C). The reaction time highly depends on steric bulk of the primary amine, but can be shortened by heating the reaction mixture.

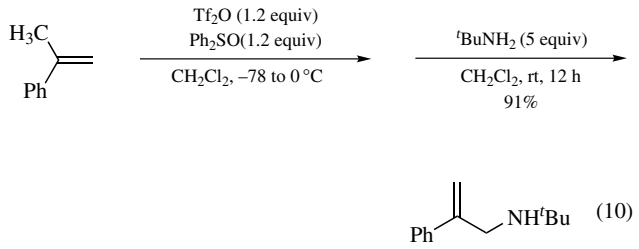
Aziridination of *trans*- and *cis*-β-methylstyrene with benzylamine gave two diastereomeric aziridines with almost the same yields and diastereomeric ratio (1:1), suggesting that the stereochemistry of aziridines is not influenced by the olefin configuration. A one step protocol can also be applied in case of unstable 2-arylethenyl(diphenyl)sulfonium salts.

Synthesis of α-Imidostyrenes. α-Imidostyrenes, useful precursors to vinylamines can be synthesized by introducing an imido group to the α-position of styrenes with the diphenyl sulfoxide-Tf_2O reagent combination.[19] Styrenes with a hydrogen atom at the α-position react with diphenyl(trifluoromethanesulfonyloxy)sulfonuim triflate to form diphenylstyrylsulfonium triflates which, in turn are converted into the corresponding α-imidostyrenes on treatment with sodium or potassium salts of cyclic imides (eq 9).

Several styrene derivatives can be used, but the presence of an electron donating group in the benzene ring diminishes the yield. The reaction time is highly dependent on the steric bulk of the cyclic imide which should be used in excess as it is in part quenched by triflic acid generated during the reaction.



Synthesis of β,γ-Unsaturated Amines. 1,1-Disubstituted alkenes can be converted into the corresponding β,γ-unsaturated amines, valuable synthons in medicinal chemistry, and versatile synthetic intermediates, via a three-step protocol with moderate to good yields. The initial formation of α,β-unsaturated diphenylsulfonium triflates from alkenes, such as α-methylstyrene, and the combination of diphenyl sulfoxide and Tf_2O, is followed by double bond migration to form β,γ-unsaturated sulfonium triflates. Subsequent nucleophilic substitution with primary or secondary amines such as *tert*-butylamine leads to the corresponding β,γ-unsaturated amines (eq 10).[20]

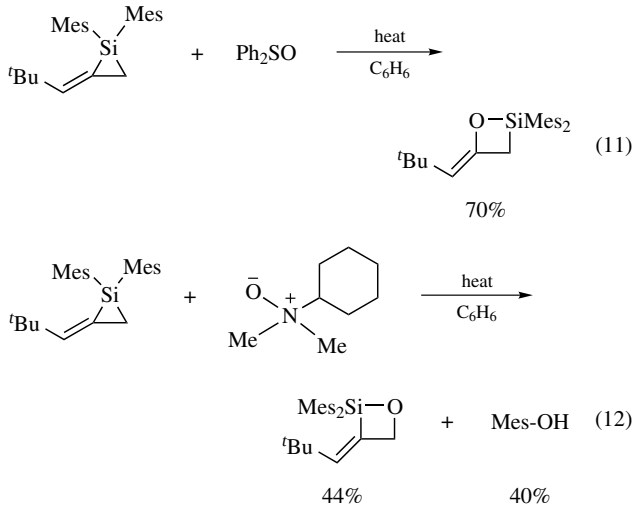


Steric hindrance at the γ-position of the alkene inhibits smooth double bond migration. For example, in case of 2-phenyl-3-methyl-1-butene, consumption of the corresponding sulfonium salt was incomplete even after prolonged reaction time or heating, and yielded only 45% of the desired product. Trisubstituted alkenes also generate the desired products, however yields are low.

Synthesis of Alkylidene 1,2-Oxasiletanes. The regiospecific oxidation of siliranes to 1,2-oxasiletanes can be accomplished in moderate yield with diphenyl sulfoxide.[21] When 1,1-dimesityl-2*Z*-neopentylidenesilirane was heated with diphenyl sulfoxide in benzene, 2,2-dimesityl-4*Z*-neopentylidene-1,2-oxasiletane was formed in 70% yield (eq 11). In contrast, use of cyclohexyldimethylamine *N*-oxide instead of diphenyl sulfoxide gave the isomeric 1,2-oxasiletane in 44% yield along with mesitol in 40% yield (eq 12).

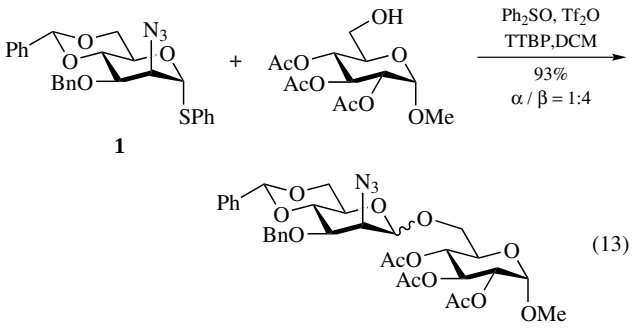
Interestingly, when the electrophilicity of the sulfur atom was lowered by introducing a *p*-methoxy group to the benzene ring of diphenyl sulfoxide, the regioselectivity dropped significantly.

The nucleophilicity of the oxygen atom should also be considered, as no reaction was observed with *p*-nitrophenyl phenyl sulfoxide. Both oxasiletanes were thermally stable and did not undergo retro [2 + 2] reaction to give silanone and olefin.



Chemoselective Glycosylation. Diphenyl sulfoxide in combination with Tf_2O provides a very potent thiophilic glycosylation promoter system, which is capable of activating highly disarmed thioglycosides and mechanistically works in a similar manner to benzenesulfinyl piperidine (BSP)/Tf_2O.[22] Glycosylation of 4,6-*O*-benzylidene, 4,6-*O*-phenylboronate, and 4,6-*O*-polystrylboronate protected galacto-, gluco-, and mannopyranosyl thioglycosides was investigated under BSP/Tf_2O and diphenyl sulfoxide/Tf_2O conditions. In all three cases both methods gave comparable yields and selectivities.[23]

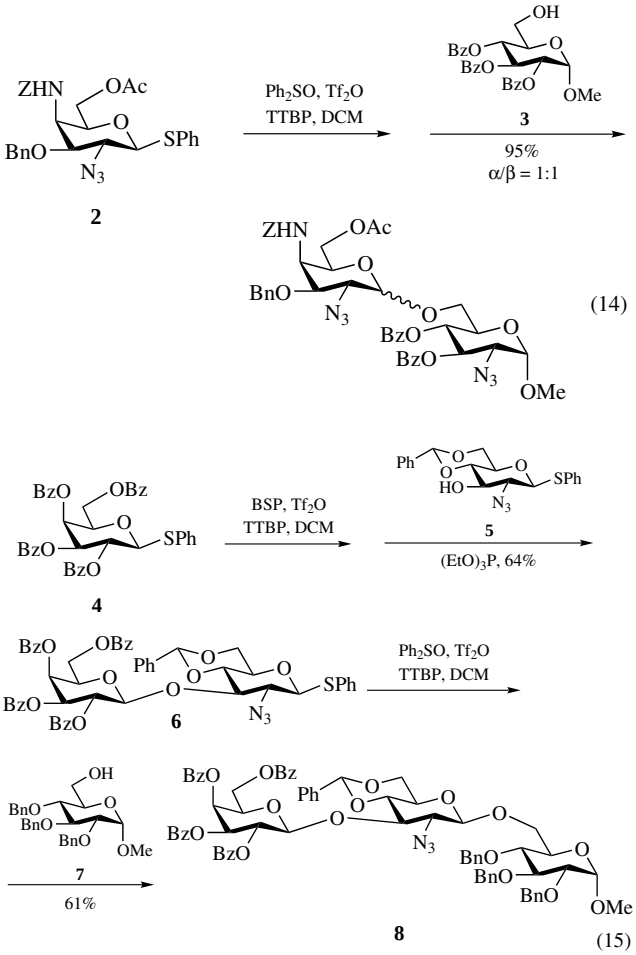
However, the BSP/Tf_2O promoter system failed to effectuate the condensation of *S*-phenyl-2-azido-3-*O*-benzyl-4,6-*O*-benzylidene thiomannoside (**1**) with a variety of acceptors, a task that was accomplished in high yield with the diphenyl sulfoxide/Tf_2O promoter system (eq 13).



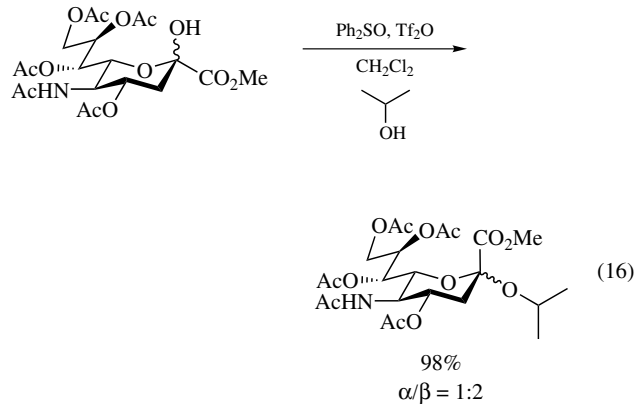
Another disarmed donor **2** was activated with diphenyl sulfoxide and Tf_2O and coupled with relatively unreactive acceptor **3** with excellent yield (eq 14).[24]

This difference in reactivity between the BSP/Tf_2O and diphenyl sulfoxide/Tf_2O reagents can be exploited in chemoselective oligosaccharide synthesis.[22,25]

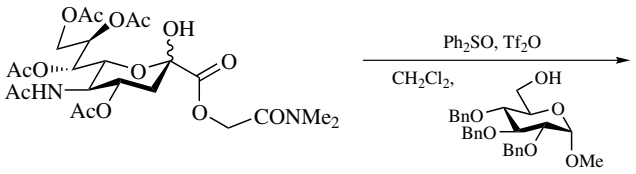
Such an application is depicted in the assembly of trisaccharide **8** (eq 15). Activation of disarmed galactose donor **4** with BSP/Tf_2O followed by treatment with highly disarmed thioglycoside acceptor **5** and quenching with $(EtO)_3P$ afforded dimer **6** with 64% yield. Subsequent diphenyl sulfoxide/Tf_2O-mediated activation and condensation with **7** furnished the trisaccharide **8** in acceptable yield (61%).[25]

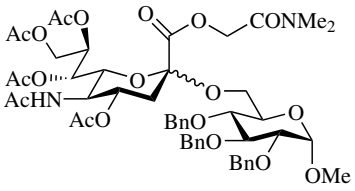


Dehydrative Sialylation. The recently developed dehydrative glycosylation of hemiacetal donors using the diphenyl sulfoxide-Tf_2O reagent combination[13] can also be employed in the preparation of the more challenging sialyl conjugates, in which anomeric bond formation occurs at the C2-ketal carbon. The anomeric selectivity however, favors the non-natural β-glycosidic linkage (eq 16).[26]



To augment the naturally-occurring, thermodynamically-disfavored α-selective sialyl conjugate, the C1-*N,N*-dimethyl glycolamide protective group can be employed. Although the proportion of α-sialoside product increases with this group, the reaction was still not sufficiently α-selective (eq 17).

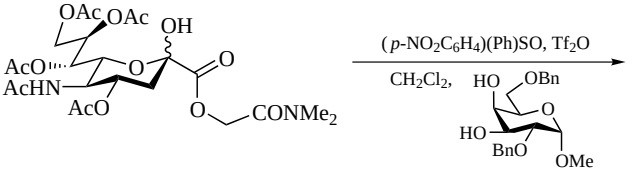


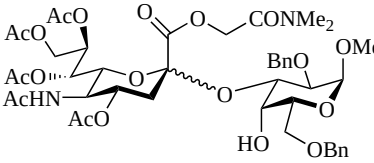


72%
α/β = 1:1

(17)

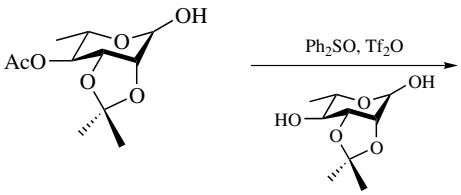
The problem can be circumvented by using an electron-deficient diaryl sulfoxide. For example, (*p*-nitrophenyl)(phenyl) sulfoxide-Tf_2O mediated dehydrative sialylation is highly stereoselective and favors the naturally occurring α-sialyl conjugate (eq 18).





57%
α/β = 10:1

(18)



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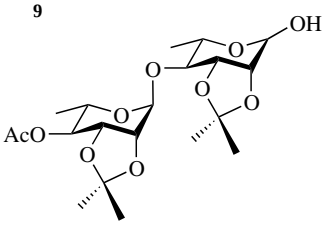
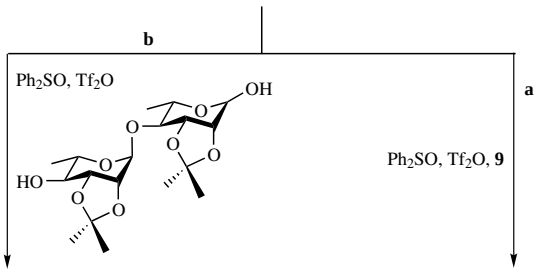


97%
α/β = 4:1



10

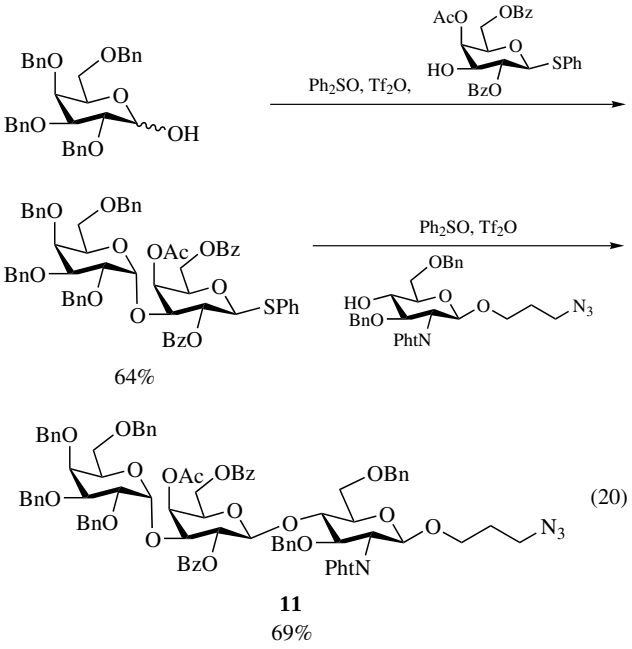
74%, α/β = 4:1[a]
87%, α/β = 4:1[b]

83%
α/β = 2:1

(19)

Iterative Dehyrdative Glycosylation. The dehydrative glycosidic coupling method using diphenyl sulfoxide-Tf_2O reagent combination[13] has been demonstrated to bring about selective activation of an armed hemiacetal in the presence of a disarmed one.[27] The scope of this chemistry is illustrated in the synthesis of a 1,4-α-linked tetrasaccharide **10** by two routes (eq 19). Route **a** shows the applicability of the iterative protocol whereas route **b** highlights the adaptability of this strategy to the block synthesis of oligosaccharides.

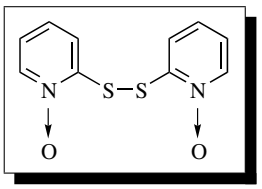
Iterative Glycosylation of 1-Hydroxy and 1-Thiodonors. The diphenyl sulfoxide-Tf_2O mediated dehydrative condensation of 1-hydroxyl donors with thioglycosides affords in good yield the thiodisaccharides, which in turn can be activated by the same activator system to furnish trisaccharides.[28] This sequential glycosylation is exemplified by the synthesis of trisaccharide **11** (eq 20). The synthesis can be conducted in a step-wise procedure (64 and 69%) as well as in a one-pot procedure (80%) with a much improved yield. Thioglycuronic acids can also be used both as donor and acceptor in the aforementioned coupling procedure toward acidic di- and trisaccharides.[29]



Related Reagents. 1-Benzenesulfinyl Piperidine; Methoxyphenyl Benzenethiosulfinate; Benzothianthrene Oxide; *N*-Iodosuccinimide; Dimethyl(methylthio)sulfonium Tetrafluoroborate.

1. Lorber, C. Y.; Pauls, I.; Osborn, J. A., *Bull. Soc. Chem. Fr.* **1996**, *133*, 755.
2. Coleman, K. S.; Bedel, L. J. L.; Osborn, J. A., *C. R. Acad. Sci. Paris, IIC* **2000**, *3*, 765.
3. Arterburn, J. B.; Nelson, S. L., *J. Org. Chem.* **1996**, *61*, 2260.
4. Arterburn, J. B.; Perry, M. C.; Nelson, S. L.; Dible, B. R.; Holguin, M. S., *J. Am. Chem. Soc.* **1997**, *119*, 9309.
5. Koide, T.; Otaka, A.; Suzuki, H.; Fujii, N., *Synlett* **1991**, 345.
6. Akaji, K.; Tatsumi, T.; Yoshida, M.; Kimura, T.; Fujiwara, Y.; Kiso, Y., *J. Chem. Soc., Chem. Commun.* **1991**, 167.
7. Akaji, K.; Tatsumi, T.; Yoshida, M.; Kimura, T.; Fujiwara, Y.; Kiso, Y., *J. Am. Chem. Soc.* **1992**, *114*, 4137.
8. Akaji, K.; Fujino, K.; Tatsumi, T.; Kiso, Y., *J. Am. Chem. Soc.* **1993**, *115*, 11384.
9. Endo, Y.; Shudo, K.; Okamoto, T., *Chem. Pharm. Bull.* **1981**, *29*, 3753.
10. Hartke, K.; Strangemann, D., *Heterocycles* **1986**, *24*, 2399.
11. Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y., *J. Am. Chem. Soc.* **1998**, *120*, 13515.
12. Honda, E.; Gin, D. Y., *J. Am. Chem. Soc.* **2002**, *124*, 7343.
13. Garcia, B. A.; Poole, J. L.; Gin, D. Y., *J. Am. Chem. Soc.* **1997**, *119*, 7597.
14. Garcia, B. A.; Gin, D. Y., *J. Am. Chem. Soc.* **2000**, *122*, 4269.
15. Nagai, U.; Sammes, P. G., *J. Chem. Soc. C* **1967**, 2230.
16. Reddy, A. S.; Reddy, B. R., *Can. J. Chem.* **1982**, *60*, 40.
17. Takuwa, T.; Onishi, Y. J.; Matsuo, J.-i.; Mukaiyama, T., *Chem. Lett.* **2004**, *33*, 8.
18. Matsuo, J.-i.; Yamanaka, H.; Kawana, A.; Mukaiyama, T., *Chem. Lett.* **2003**, *32*, 392.
19. Yamanaka, H.; Mukaiyama, T., *Chem. Lett.* **2003**, *32*, 1192.
20. Yamanaka, H.; Matsuo, J.-i.; Kawana, A.; Mukaiyama, T., *Chem. Lett.* **2003**, *32*, 626.
21. Saso, H.; Yoshida, H.; Ando, W., *Tetrahedron Lett.* **1988**, *29*, 4747.
22. Codée, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A., *Org. Lett.* **2003**, *5*, 1519.
23. Crich, D.; de la Mora, M.; Vinod, A. U., *J. Org. Chem.* **2003**, *68*, 8142.
24. van den Bos, L. J.; Codée, J. D. C.; van Boom, J. H.; Overkleeft, H. S.; van der Marel, G. A., *Org. Biomol. Chem.* **2003**, *1*, 4160.
25. Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A., *Tetrahedron* **2004**, *60*, 1057.
26. Haberman, J. M.; Gin, D. Y., *Org. Lett.* **2003**, *5*, 2539.
27. Nguyen, H. M.; Poole, J. L.; Gin, D. Y., *Angew. Chem., Int. Ed.* **2001**, *40*, 414.
28. Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A., *Org. Lett.* **2003**, *5*, 1947.
29. van den Bos, L. J.; Codée, J. D. C.; van der Toorn, J. C.; Boltje, T. J.; van Boom, J. H.; Overkleeft, H. S.; van der Marel, G. A., *Org. Lett.* **2004**, *6*, 2165.

2,2′-Dipyridyl Disulfide-*N*,*N*′-dioxide



[7275-43-6] $C_{10}H_8N_2O_2S_2$ (MW 252.32)

InChI = 1/C10H8N2O2S2/c13-11-7-3-1-5-9(11)15-16-10-6-2-4-8-12(10)14/h1-8H

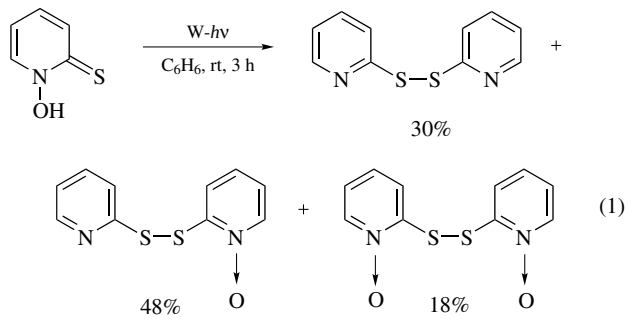
InChIKey = ZHDBTKPXEJDTTQ-UHFFFAOYAK

(reagent used for the preparation of *O*-acyl thiohydroxamates (Barton esters), which are the precursors of mainly sp^3 carbon-centered radicals formed via decarboxylation of acyloxyl radicals)

Physical Data: mp 205–206 °C[1] (white crystalline solid).

Analysis of Reagent Purity: ^{1}H-NMR ($CDCl_3$, TMS): $\delta = 8.28$ (2H, d), 7.58 (2H, d), 7.22 (4H, m). ^{13}C-NMR: $\delta = 148.5$, 138.7, 126.6 (d), 122.5 (d), 121.9 (d).

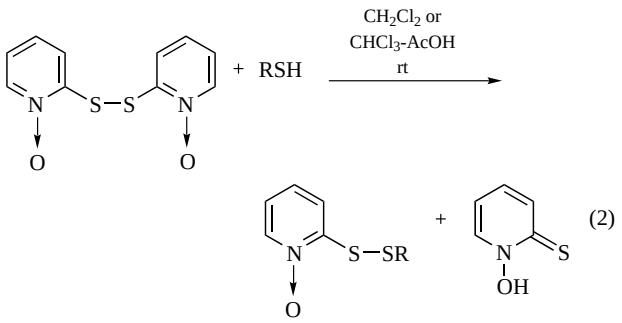
Preparative Methods: generally, 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide is obtained by the oxidation of *N*-hydroxypyridine-2-thione (2-mercaptopyridine-1-oxide, thiohydroxamic acid). To a suspension of 42.3 g of *N*-hydroxypyridine-2-thione in water (300 mL) was added 30% hydrogen peroxide (35 mL). The reaction is slightly exothermic. The reaction mixture was stirred for 1 h with the temperature maintained at 45 °C. A white solid, 34.6 g (81%), was collected by filtration (mp 200–201 °C). Recrystallization from methanol gave white crystals (mp 205–206 °C).[1a,2] Other preparative methods include irradiation of *N*-hydroxypyridine-2-thione with a tungsten lamp (500 W) in benzene which affords a mixture of 2,2′-dipyridyl disulfide, 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide, and its mono-*N*-oxide (eq 1).[3a] The mono-*N*-oxide is rather unstable and undergoes disproportionation to form dipyridyl disulfide and 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide.[3] Photolysis (350 nm) of *N*-hydroxypyridine-2-thione with a mercury lamp provides 2,2′-dipyridyl disulfide (7%), 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide (38%), and its mono-*N*-oxide (15%), together with 2-pyridinesulfonic acid (22%).[3]



(1)

Handling, Storage, and Precaution: air-stable solid.

Preparation of Disulfides. Unsymmetrical alkyl and aryl pyridyl disulfide-*N*-oxides are prepared by the reaction of 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide with various thiols in good yields (eq 2).[2] *N*-hydroxypyridine-2-thione is a by-product of this reaction.

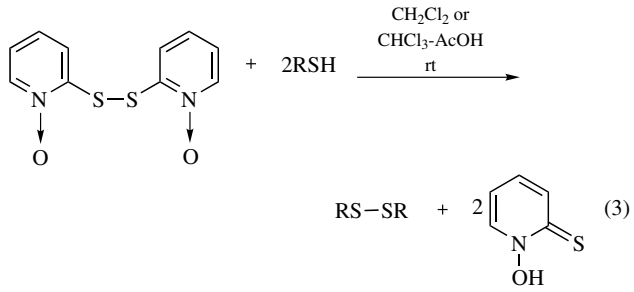


(2)

R	Time (h)	Yield (%)
n-C_3H_7	30	100
CH_2CO_2H	12	98
$CH_2CH(NHAc)CO_2H$	30	96

Alkyl and aryl pyridyl disulfide-*N*-oxides are also effective sulfenylating agents. Thus, treatment under prolonged reaction time of 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide with 2 equiv of thiol generates symmetrical disulfides and *N*-hydroxy-2-thiopyridone as shown in eq 3.[2]

Preparation of *O*-Acyl Thiohydroxamates (Barton Esters). *O*-Acyl esters (Barton esters) of *N*-hydroxypyridine-2-thione are excellent precursors of carbon-centered radicals through the rapid decarboxylation of the acyloxyl radicals formed, under mild reaction conditions (photolysis with a tungsten lamp at room temperature, or refluxing in benzene or toluene). Carbon-centered radicals formed in this manner can be used for various types of functional group conversions and C-C bond formations (Figure 1).[4]



(3)

R	Time (h)	Yield (%)
CH_2CO_2H	18	100
C_6H_5	54	92

N-Hydroxypyridine-2-thione derivatives such as carbamates and carbonates are also precursors of nitrogen- and oxygen-centered radicals. Generally, Barton esters are prepared from (a) acid chlorides with *N*-hydroxypyridine-2-thione in the presence of a base, (b) carboxylic acids and *N*-hydroxypyridine-2-thione with DCC, (c) carboxylic acids and *N*-hydroxypyridine-2-thione with isobutyl chloroformate via mixed anhydrides, (d) carboxylic acids with a salt prepared from sodium salt of *N*-hydroxypyridine-2-thione and phosgene, in the presence of a base. These methods are applicable to a wide variety of carboxylic acids including those derived from peptides and nucleosides. However, for very sensitive carboxylic acids, reductive condensation with 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide and a phosphine is effective for the preparation of Barton esters. A particular advantage of this reagent combination is the polar nature of the reagents and by-products which enables the Barton ester to be rapidly eluted from a silica gel column, thereby minimizing decomposition. Accordingly, treatment of primary, secondary, and tertiary carboxylic acids with 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide and tributylphosphine under dark conditions at room temperature provides the corresponding *O*-acyl esters of *N*-hydroxy-2-thiopyridone in high yields (eq 4).[5]

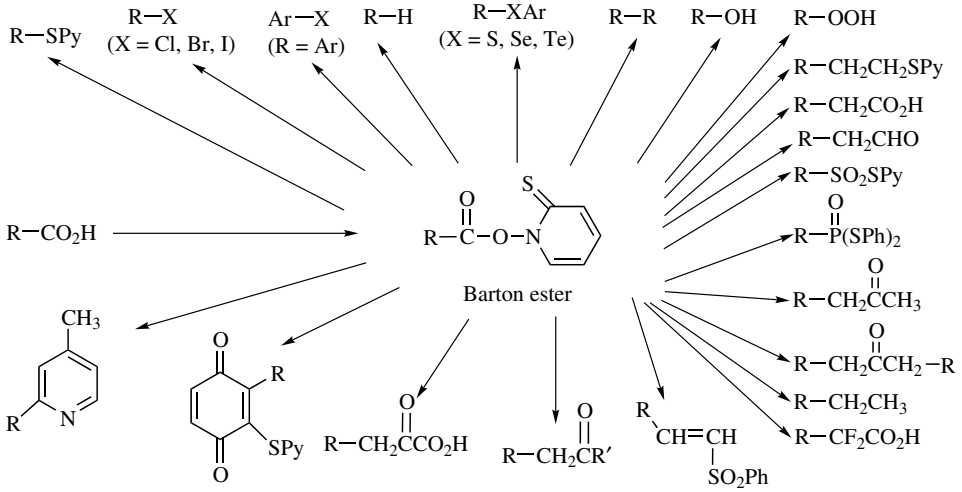
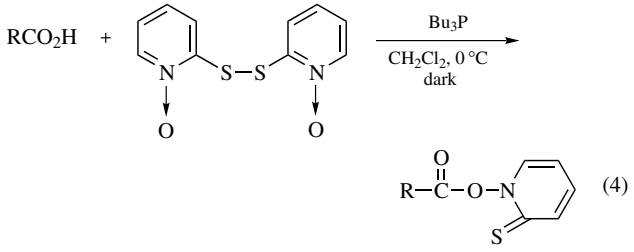
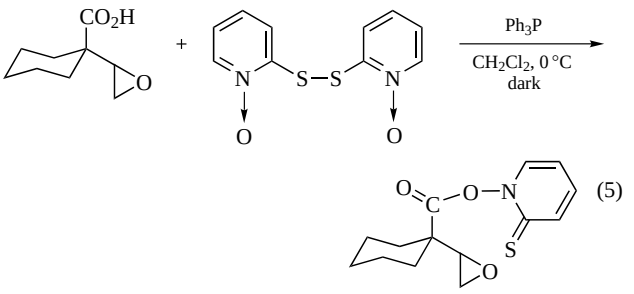


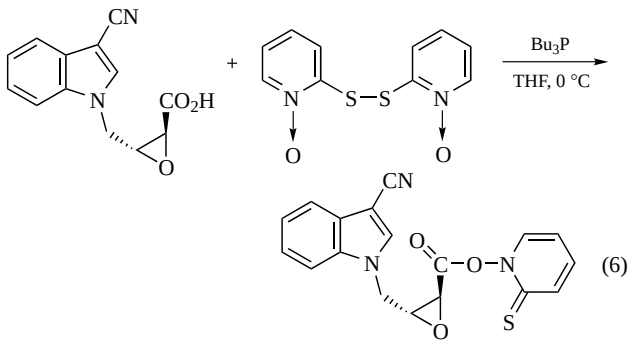
Figure 1 Functional group introduction and C-C bond formation using Barton esters

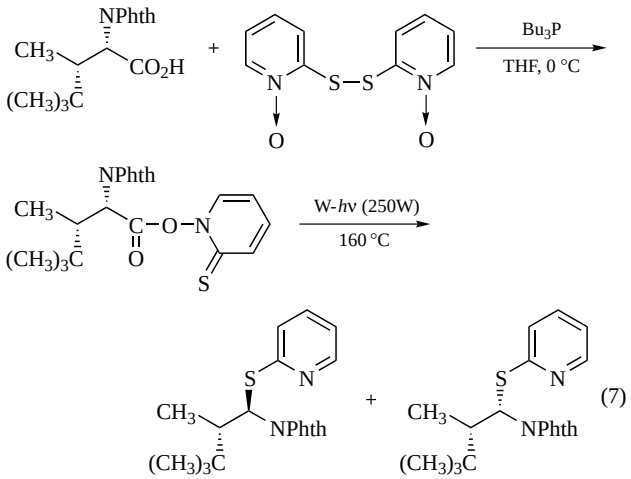


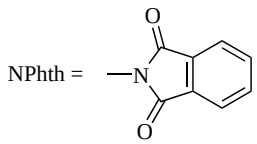
R	Yield (%)
2-phenylethyl	92
cyclohexyl	86
1-adamantyl	84

Examples of carboxylic acids containing sensitive functional groups that have been successfully converted to Barton esters in this manner are given in eqs 5–7.[6]

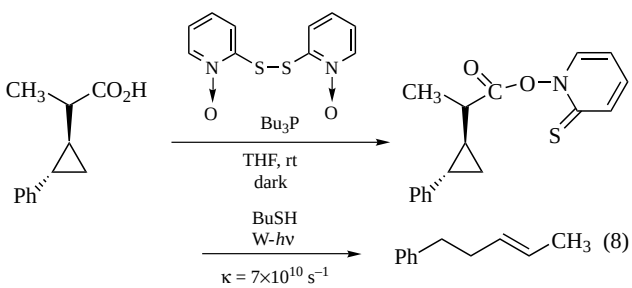




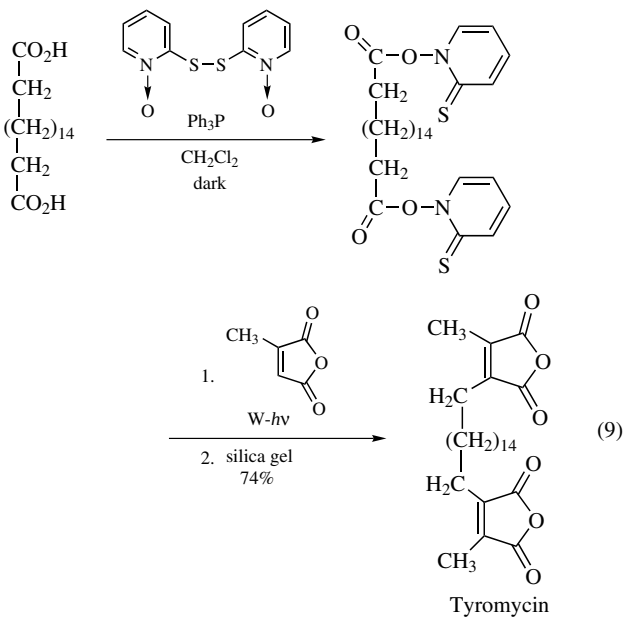




Barton esters prepared with 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide and tributylphosphine have been used for the determination of the rate constants for the *5-exo-trig* ring-closure of *N*-allyl amide radicals and for the ring-opening of cyclopropylmethyl radicals (eq 8).[7]



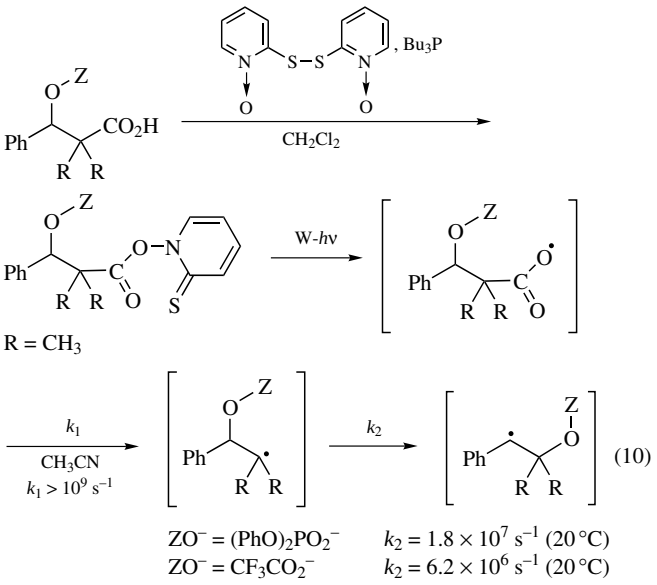
The natural product tyromycin was prepared in a good yield by the photolytic treatment of the double Barton ester of a dicarboxylic acid with a tungsten lamp (500 W) in the presence of citranic anhydride (eq 9).[8]



(9)

Tyromycin

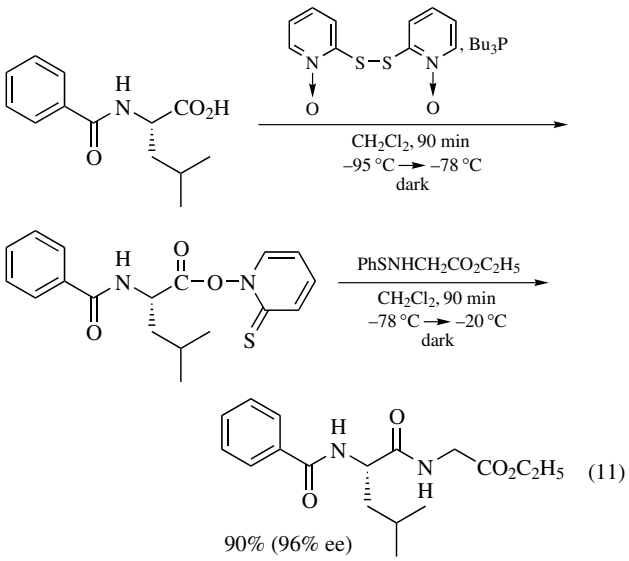
In connection with studies on the mechanism of DNA degradation by anti-cancer agents such as bleomycin and enediyne antibiotics, model systems with Barton esters bearing a phosphatoxy bleomycin and enediyne antibiotics, as well as model systems with Barton esters bearing a phosphatoxy group and related functional groups at the β-position, have been investigated in detail.[9] In this chemistry, the Barton esters were again prepared with 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide and tributylphosphine (eq 10).



(10)

$ZO^- = (PhO)_2PO_2^-$ $\quad k_2 = 1.8 \times 10^7\ s^{-1}$ (20 °C)
$ZO^- = CF_3CO_2^-$ $\quad k_2 = 6.2 \times 10^6\ s^{-1}$ (20 °C)

Finally, Barton esters formed in this manner react in situ with benzenesulfenamides at low temperatures to give amides with no racemization. The by-product of this reaction is an unsymmetrical pyridyl disulfide-*N*-oxide. This reaction is exemplified by the treatment of amino acids with 2,2′-dipyridyl disulfide-*N*,*N*′-dioxide and tributylphosphine, followed by the addition of a sulfenamide, which provides racemization-free peptides (eq 11).[10]



(11)

Related Reagents. 2,2-Dipyridyl Disulfide (a reductive condensation reagent system with triphenylphosphine); *N*-Hydroxypyridine-2-thione.

1. (a) U.S. Pat. 2,742,476 (to Bernstein, J.; Losee, K. A.) (1956) (*Chem. Abstr.* **1956**, *50*, 89530). (b) U.S. Pat. 3,700,676 (to Damico, R. A.) (1972) (*Chem. Abstr*. **1973**, *78*, 43278z).
2. Barton, D. H. R.; Chen, C.; Wall, G. M., *Tetrahedron* **1991**, *47*, 6127.
3. (a) Boivin, J.; Crépon, E.; Zard, S. Z., *Tetrahedron Lett.* **1990**, *31*, 6869. (b) Barton, D. H. R.; Jaszberenyi, J. C.; Morrell, A. I., *Tetrahedron Lett.* **1991**, *32*, 311. (c) Adam, W.; Grimm, G. N.; Marquardt, S.; Saha-Möller, C. R., *J. Am. Chem. Soc.* **1999**, *121*, 1179.
4. (a) Crich, D., *Aldrichimica Acta* **1987**, *20*, 35. (b) Barton, D. H. R., *Aldrichimica Acta* **1990**, *23*, 3.
5. Barton, D. H. R.; Samadi, M., *Tetrahedron* **1992**, *48*, 7083.
6. (a) Ziegler, F. E.; Harran, P. G., *Tetrahedron Lett.* **1993**, *34*, 4505. (b) Damm, W.; Hoffmann, U.; Macko, L.; Neuburger, M.; Zehnder, M.; Giese, B., *Tetrahedron* **1994**, *50*, 7029. (c) Krishnamurthy, V.; Rawal, V. H., *J. Org. Chem.* **1997**, *62*, 1572.
7. (a) Musa, O. M.; Horner, J. H.; Newcomb, M., *J. Org. Chem.* **1999**, *64*, 1022. (b) Choi, S.-Y.; Toy, P. H.; Newcomb, M., *J. Org. Chem.* **1998**, *63*, 8609.
8. Poigny, S.; Guyot, M.; Samadi, M., *J. Org. Chem.* **1998**, *63*, 1342.
9. (a) Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X.; Newcomb, M.; Whitted, P. O., *Tetrahedron* **1999**, *55*, 3317. (b) Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X.; Yao, Q.; Zipse, H., *J. Am. Chem. Soc.* **1999**, *121*, 10685. (c) Newcomb, M.; Miranda, N.; Huang, X.; Crich, D., *J. Am. Chem. Soc.* **2000**, *122*, 6128. (d) Crich, D.; Huang, X.; Newcomb, M., *J. Org. Chem.* **2000**, *65*, 523. (e) Bales, B. C.; Horner, J. H.; Huang, X.; Newcomb, M.; Crich, D.; Greenberg, M. M., *J. Am. Chem. Soc.* **2001**, *123*, 3623. (f) Horner, J. H.; Taxil, E.; Newcomb, M., *J. Am. Chem. Soc.* **2002**, *124*, 5402.
10. Barton, D. H. R.; Ferreira, J. A., *Tetrahedron* **1996**, *52*, 9367.

Hideo Togo
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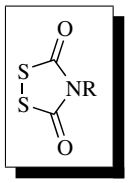
1,2,4-Dithiazolidine-3,5-dione



(**1**; R = H)
[35371-97-2] $C_2HNO_2S_2$ (MW 135.16)
InChI = 1/C2HNO2S2/c4-1-3-2(5)7-6-1/h(H,3,4,5)/f/h3H
InChIKey = BPVALDZRWMHTCJ-TULZNQERCC
(**2**; R = K) $C_2NO_2S_2K$ (MW 173.26)
InChI = 1/C2HNO2S2.K/c4-1-3-2(5)7-6-1;/h(H,3,4,5);/q;+1/p-1/fC2NO2S2.K/q-1;m
InChIKey = FFHZHAQLNGYGBX-RXMVNNPPCP

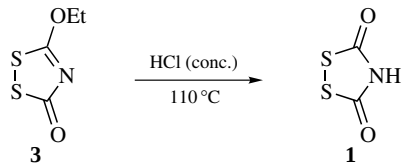
(heterocyclic system used as a protecting group for primary amines. Reagents **1** and **2** both used as a nucleophilic, protected primary amine, or isocyanate equivalent. Reagent **1** can be used for oxidative sulfurization of phosphorus(III) species)

Physical Data: **1** mp 141–143 °C; *d* 1.880 g cm^{-3} (calculated from crystallographic data); pK_a 2.85 (H_2O, I = 0.5, 25 °C). **2** mp 170–180 °C (some decomposition observed at 140–142 °C); *d* 2.100 g cm^{-3} (calculated from crystallographic data).

Solubility: **1** is soluble in most common organic solvents, except those of very low polarity. **2** is soluble in *N*,*N*-dimethylformamide, acetonitrile, and ethanol.

Form Supplied in: At the time of writing, neither **1** nor **2** is commercially available. Purification details for both compounds are given below.

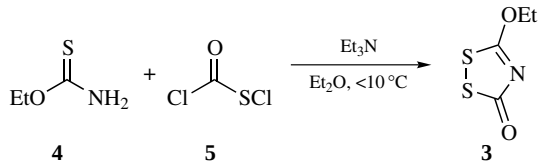
Preparative Method: The parent heterocycle **1** can be readily prepared on a multigram scale by acidic hydrolysis of 3-ethoxy-1,2,4-dithiazolin-5-one **3** (eq 1).[1–3]



(1)

3 **1**

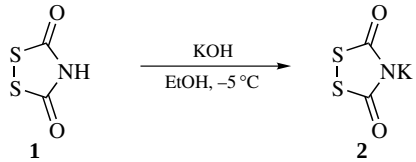
The latter reagent is obtained from the reaction between ethyl thiocarbamate (**4**) and commercially available chlorocarbonylsulfenyl chloride (**5**) in the presence of triethylamine (eq 2).[1–3] The outcome of this key reaction is highly solvent dependent, with anhydrous diethyl ether giving the optimum yield, while also minimizing the formation of unwanted by-products.[2,3] (Note: Reference [3] details the fully optimized preparations of **3** and **1**).



(2)

4 **5** **3**

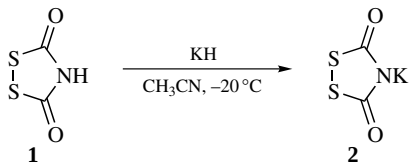
Two methods facilitate the preparation of the potassium salt **2** of **1**.[4] Firstly in a procedure analogous to that used in the preparation of potassium phthalimide,[5] **2** can be obtained by treatment of **1** with an equimolar quantity of ethanolic potassium hydroxide (eq 3).



(3)

1 **2**

Alternatively, potassium hydride can be used as the base in anhydrous acetonitrile solvent (eq 4).



(4)

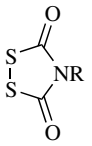
1 **2**

In both cases, analytically pure material can be obtained by recrystallization of the crude product from ethanol–diethyl ether.

Purification: **1** recrystallization from toluene. **2** recrystallization from ethanol–diethyl ether.

Handling, Storage, and Precautions: **1** in its crystalline state can be stored at room temperature in air for at least 2 years without detectable decomposition. Stability studies have not been reported on **2** although it can certainly be stored for several days under vacuum at room temperature, after recrystallization. No particular hazards, handling problems, or precautions have been reported for the use of either **1** or **2**. This is, however, most likely to be a result of no detailed safety testing having been carried out and hence appropriate care should be taken in their use.

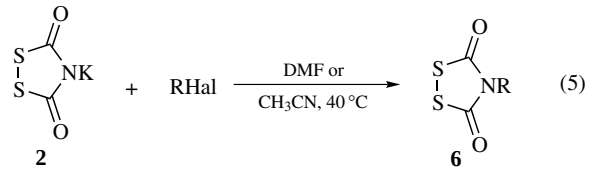
Reactions at the Nitrogen Atom. The 1,2,4-dithiazolidine-3,5-dione heterocyclic system can be regarded as a moiety for the protection of two reactive functional groups, the primary amine and the isocyanate, and hence *N*-alkylated derivatives (**6**) can be regarded as containing either of these two groups in a masked form.



(**6**; R = alkyl, aryl, etc.)

These *N*-alkylated derivatives are often referred to as dithiasuccinoyl (Dts) imides with compounds of structure **6** being abbreviated to R-NDts.

***N*-Alkylation of Potassium 1,2,4-Dithiazolidine-3,5-dione (2).** The most direct method for the preparation of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones (**6**) uses the straightforward nucleophilic displacement reaction between potassium 1,2,4-dithiazolidine-3,5-dione (**2**) and an alkyl halide[4,6] in a procedure analogous to the *N*-alkylation of potassium phthalimide in the traditional Gabriel synthesis of primary amines[7] (eq 5).



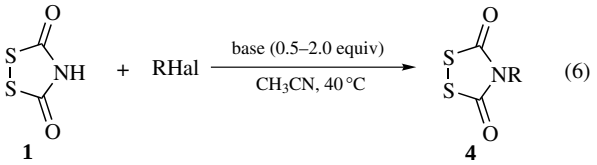
2 **6**

(Hal = Br or I)

Reasonable yields can be obtained with primary alkyl halides (e.g., methyl iodide, ^{n}hexyl iodide) and more reactive alkylating agents (e.g., benzyl bromide), with secondary and lower reactivity halide substrates being less satisfactory. Both DMF and acetonitrile are suitable solvents for this transformation.

This *N*-alkylation methodology can also be used in solid-supported applications.[4]

N-Alkylation of 1,2,4-Dithiazolidine-3,5-dione (1). The very low pK_a value of **1** (pK_a = 2.85[6]) compared with other imides such as phthalimide (typically ca. 9.5–10) facilitates *N*-deprotonation with a wide range of bases. These include sodium or potassium hydride, sodium acetate, sodium bicarbonate, potassium *tert*-butoxide, and caesium carbonate. The optimum stoichiometry of **1** to base is dependent on the base and alkyl halide in question, with acetonitrile proving to be the preferred solvent (eq 6).[4]

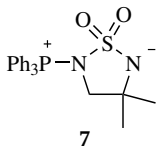


1 **4**

(Hal = Br or I)

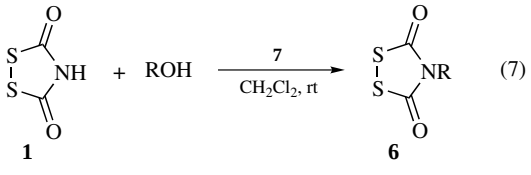
As with *N*-alkylations of potassium salt **2**, primary and inherently reactive alkyl halides provide the better results. Alkyl chlorides may also be used, provided that tetrabutylammonium bromide or (preferably) potassium iodide is added, to provide nucleophilic catalysis.

Mitsunobu-type N-Alkylation of 1,2,4-Dithiazolidine-3,5-dione (1). Despite its high acidity suggesting that it should be an excellent nucleophile in Mitsunobu displacement reactions of alcohols (cf. phthalimide.[8–10]), the parent heterocycle **1** is degraded by the triphenylphosphine used in this process (see later). Similar stereoselective displacement reactions of alcohols with **1** can, however, be mediated using the readily prepared betaine reagent **7**.[11,12]



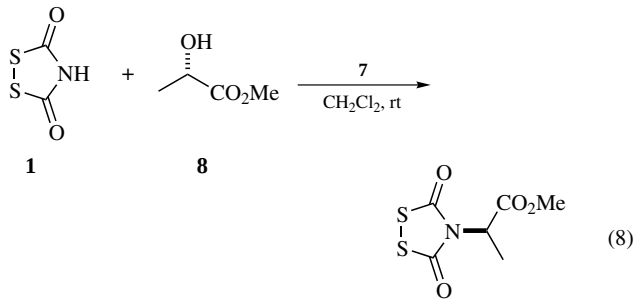
7

A variety of primary and secondary alcohols have been shown to undergo displacement with **1** mediated by **7** (eq 7).[13,14] Dichloromethane is the solvent of choice for this transformation, **7** being essentially insoluble in THF.



1 **6**

Yields are largely comparable with standard Mitsunobu reactions between alcohols and phthalimide, with enantiomeric excesses varying from 69 to 97%, depending on the alcohol substrate.[14] For example, using *S*-methyl lactate (**8**), **6a** was obtained in a 52% yield, the product **6a** exhibiting an ee of 92% (eq 8).



1 **8**

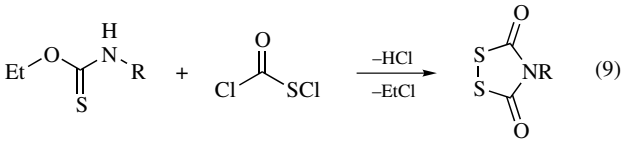
52%, 92% ee

6a

In comparison, a standard Mitsunobu reaction between *S*-ethyl lactate and phthalimide gave a 45% yield of the expected protected D-alanine derivative with an ee greater than 99%,[15] while Barrett's modified method using potassium phthalimide and an imidate ester gave a 25% yield with racemization.[16] (Note: Less than complete inversion of configuration has been noted with the use of **7** as a Mitsunobu-type reagent.[11])

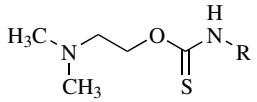
Alternative Routes to N-Alkylated 1,2,4-Dithiazolidine-3,5-diones (6). It should be noted that the routes *N*-alkylated 1,2,4-dithiazolidine-3,5-diones (**6**) described above may not always be appropriate, and alternative methods that do not employ **1** or **2** directly may also be used.

In early studies into the use of the dithiasuccinoyl (Dts) primary amine protecting group, the desired *N*-alkylated derivatives (**6**) were prepared from the reaction between *O*-ethyl-*N*-alkyl (or aryl) thiocarbamates (**9**) and chlorocarbonylsulfenyl chloride (**5**) (eq 9).[17]



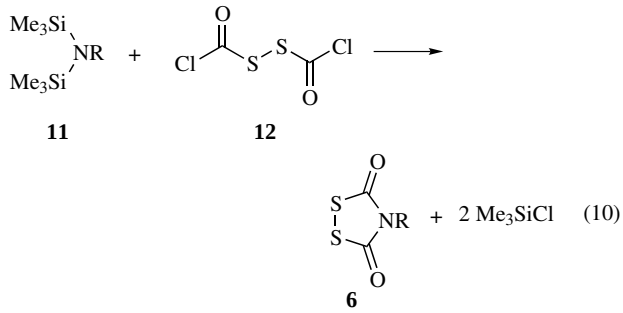
9 **5** **6**

Problems associated with the formation of by-products in this procedure can be alleviated by the use of *O*-dimethylaminoethyl-*N*-alkyl (or aryl) thiocarbamates (**10**) in place of the *O*-ethyl derivatives (**9**).[18] In this modification, most of the by-products can be removed using an aqueous acid extraction.



10

More recently, it has been shown that *N*-alkyl and aryl 1,2,4-dithiazolidine-3,5-diones (**6**) can also be accessed directly from the reaction between bis(trimethylsilyl)amines (**11**) and bis (chlorocarbonyl)disulfane (**12**) (eq 10).[19]

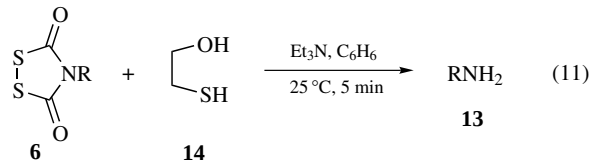


11 **12** **6**

(10)

Reactions at the Sulfur Atoms. The majority of the key synthetic applications of this heterocyclic system are focused on the reactivity of the disulfide linkage toward nucleophiles. Three such applications are described.

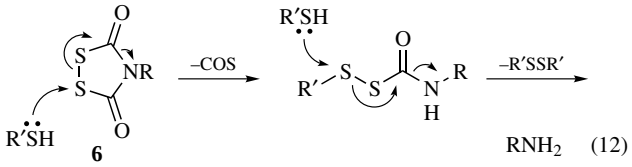
The Dts Imide Protecting Group. The dithiasuccinoyl (Dts) moiety represents a potentially very useful protecting group for both N–H bonds of a primary amine **13** as R–NDts in structure **6**. Its strength lies in the fact that it is very stable toward the acidolytic conditions commonly used to cleave *tert*-butyl-based protecting groups (e.g., *tert*-butyl esters, *tert*-butoxycarbonyl protected amines), mild base ($NaHCO_3$), and also photolysis at wavelengths above 330 nm. It can, however, be cleaved by thiolysis (accelerated by the addition of tertiary amines) (eq 11).[17]



6 **14** **13**

(11)

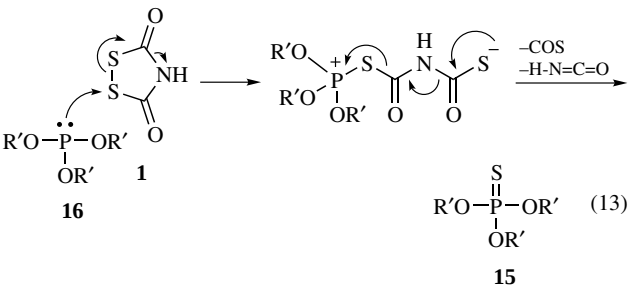
Its use is, therefore, applicable in orthogonal protection strategies. To this end it has, for example, been used in solid-phase peptide synthesis,[20] the preparation of protected peptide nucleic acid oligomers,[21] and for the protection of aminoglycosides.[22] 2-Mercaptoethanol (**14**) in combination with triethylamine has often been used as the deprotecting reagent although a range of other thiols/conditions also lead to rapid, quantitative deprotection.[23] The kinetics and mechanism of the thiolytic cleavage have been examined in detail.[23] A simplistic version of this mechanism is shown in eq 12, the first step involving nucleophilic attack at the disulfide moiety of the 1,2,4-dithiazolidine-3,5-dione heterocycle by the thiol.



6 **13**

(12)

1,2,4-Dithiazolidine-3,5-dione (1) as a Sulfur-transfer Reagent. The importance of phosphorothioate derivatives (**15**) in nucleic acid research has led to the development of methods for the oxidative sulfurization of phosphorus(III) systems using sulfur-containing heterocycles such as 1,2,4-dithiazolidine-3,5-dione (**1**) as the sulfur-transfer reagent.[24] The mechanistic rationale for this reaction involves direct attack of the phosphorus(III) species (**16**) at one of the sulfur atoms of **1**, the by-products of the reaction being carbonyl sulfide and isocyanic acid (eq 13).[24]

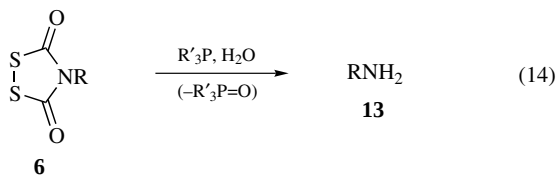


16 **1** **15**

(13)

This method is fully compatible with modern methods of automated DNA synthesis and it should be noted that 3-ethoxy-1,2,4-dithiazolin-5-one (**3**) (known as "EDITH") and other structurally related heterocycles[25] can also be used to effect the same transformation.

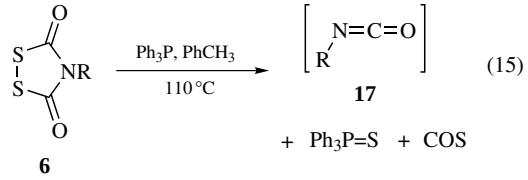
N-Alkylated 1,2,4-Dithiazolidine-3,5-diones (6) as Protected Isocyanates. The sulfur-transfer reaction described above lays the foundation for this use of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones (**6**). If *N*-alkylated 1,2,4-dithiazolidine-3,5-diones (**6**) are treated with a trialkyl- or triarylphosphine in the presence of water, the corresponding primary amine (**13**) is obtained along with the phosphine oxide (eq 14).[26]



6 **13**

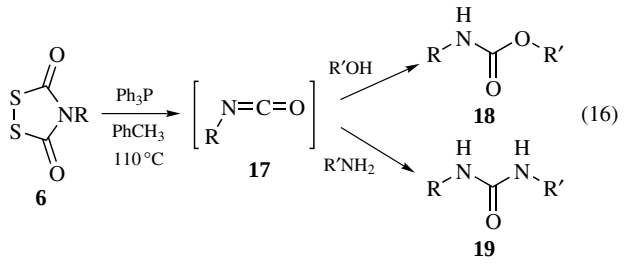
(14)

This procedure can be regarded as complementary to the thiolytic cleavage of the Dts imide protecting group. If, however, the reaction is carried out with triphenylphosphine at 110 °C, under strictly anhydrous conditions, using toluene as solvent, the *N*-alkylated heterocycle is converted into the corresponding isocyanate **17** with concomitant formation of triphenylphosphine sulfide and carbonyl sulfide (eq 15).[4,6,13,14,24,27]



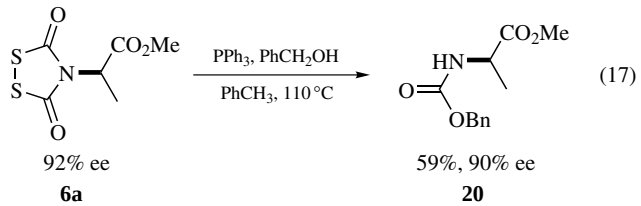
(15)

While the isocyanates **17** formed by such reactions can be isolated in a pure state,[27] their inherent reactivity means that it is often more convenient to trap them with an appropriate reaction in situ. The addition of either an alcohol or an amine to the reaction mixture facilitates the preparation of urethanes **18** or ureas **19**, respectively (eq 16).[4,6,13,14]



(16)

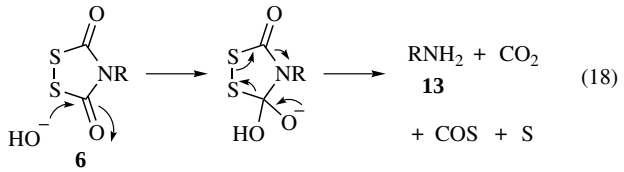
For cases where the 1,2,4-dithiazolidine-3,5-dione moiety is attached to a chiral center, there is (within experimental error) no loss of stereochemical integrity during the isocyanate formation/trapping sequence. For example, **6a** derived from *S*-methyl lactate, possessing an enantiomeric excess of 92% (see eq 8), can be converted in a 59% yield into the protected D-alanine methyl ester (**20**), which retains an enantiomeric excess of 90% (eq 17).



(17)

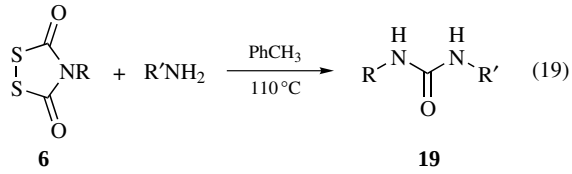
Solid-supported applications of this methodology are also possible.[4]

Reactions at the Carbonyl Group. The alkaline hydrolysis of the 1,2,4-dithiazolidine-3,5-dione heterocycle in *N*-alkylated derivatives (**6**) occurs via attack of hydroxide at the carbonyl group (eq 18).[23] As a result, such compounds cannot be subjected to strongly alkaline conditions.



(18)

Nitrogen nucleophiles also attack at the carbonyl group, giving rise to ureas. While this reaction can be a problematic side reaction if both a primary amine and a Dts imide protecting group are present within the same molecule,[21] it can also be used in a direct synthesis of ureas **19** (eq 19).[4] (It should be noted that the yields of ureas obtained using this procedure are generally lower than those obtained via an isocyanate intermediate as shown in eq 16).



(19)

Related Reagents. Phthalimide; Potassium Phthalimide.

1. Zumach, G.; Kühle, E., *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 54.
2. Dahms, G.; Haas, A.; Klug, W., *Chem. Ber.* **1971**, *104*, 2732.
3. Chen, L.; Thompson, T. R.; Hammer, R. P.; Barany, G., *J. Org. Chem.* **1996**, *61*, 6639.
4. Wood, M. E.; Cane-Honeysett, D. J.; Dowle, M. D.; Coles, S. J.; Hursthouse, M. B., *Org. Biomol. Chem.* **2003**, *1*, 3015.
5. Salzberg, P. L.; Supniewski, J. V., *Org. Synth., Coll. Vol.* **1932**, *1*, 119.
6. Cane-Honeysett, D. J.; Dowle, M. D.; Wood, M. E., *Synlett* **2000**, 1622.
7. Gibson, M. S.; Bradshaw, R. W., *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919.
8. Mitsunobu, O., *Synthesis* **1981**, 1.
9. Hughes, D. L., *Org. React.* **1992**, *42*, 335.
10. Hughes, D. L., *Org. Prep. Proced. Int.* **1996**, *28*, 127.
11. Castro, J. L.; Matassa, V. G.; Ball, R. G., *J. Org. Chem.* **1994**, *59*, 2289.
12. Brummond, K. M.; Lu, J. L., *J. Org. Chem.* **1999**, *64*, 1723.
13. Wood, M. E.; Cane-Honeysett, D. J.; Dowle, M. D., *J. Chem. Soc., Perkin Trans 1* **2002**, 2046.
14. Cane-Honeysett, D. J.; Dowle, M. D.; Wood, M. E., *Tetrahedron* **2005**, *61*, 2141.
15. Arnold, L. D.; Assil, H. I.; Vederas, J. C., *J. Am. Chem. Soc.* **1989**, *111*, 3973.
16. Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Koike, N.; Procopiou, P. A., *J. Org. Chem.* **1998**, *63*, 6273.
17. Barany, G.; Merrifield, R. B., *J. Am. Chem. Soc.* **1977**, *99*, 7363.
18. Slomczyńska, U.; Barany, G., *J. Heterocycl. Chem.* **1984**, *21*, 241.
19. Barany, M. J.; Hammer, R. P.; Merrifield, R. B.; Barany, G., *J. Am. Chem. Soc.* **2005**, *127*, 508.
20. Albericio, F.; Barany, G., *Int. J. Peptide Protein Res.* **1987**, *30*, 177.
21. Planas, M.; Bardajía, E.; Jensen, K. J.; Barany, G., *J. Org. Chem.* **1999**, *64*, 7281.
22. Meinjohanns, E.; Vargas-Berenguel, A.; Meldal, M.; Paulsen, H.; Bock, K., *J. Chem. Soc., Perkin Trans 1* **1995**, 2165.
23. Barany, G.; Merrifield, R. B., *J. Am. Chem. Soc.* **1980**, *102*, 3084.
24. Xu, Q.; Musier-Forsyth, K.; Hammer, R. P.; Barany, G., *Nucleic Acids Res.* **1996**, *24*, 1602.
25. Zhang, Z.; Nichols, A.; Tang, J. X.; Han, Y.; Tang, J. Y., *Tetrahedron Lett.* **1999**, *40*, 2095.
26. Barany, G.; Merrifield, R. B., *Anal. Biochem.* **1979**, *95*, 160.
27. Dowle, M. D., PhD Thesis, *University of London*, 1976.

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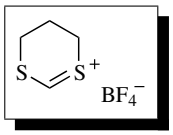
1,3-Dithienium Tetrafluoroborate



[39915-66-7] $C_4H_7BF_4S_2$ (MW 206.03)

InChI = 1/C4H7S2.BF4/c1-2-5-4-6-3-1;2-1(3,4)5/h4H,1-3H2;/q+1;-1

InChIKey = ALMBDVYVZBPKAH-UHFFFAOYAS

(reagent used for introduction of the dithiane function by electrophilic substitution; formyl equivalent by hydrolysis or methyl equivalent by reductive desulfurization for one-carbon homologation)

Alternate Name: 4*H*-1,3-dithiin-1-ium, 5,6-dihydro-, tetrafluoroborate (1–).

Physical Data: yellow solid; mp 188–190 °C.[1]

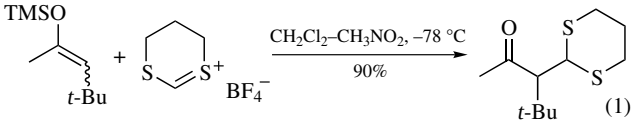
Solubility: soluble in CH_2Cl_2–CH_3NO_2 mixtures and CH_3CN.

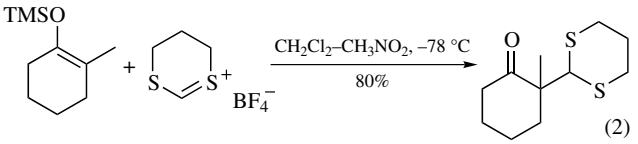
Analysis of Reagent Purity: ^{1}H NMR (CD_3NO_2) δ 11.10 (s, 1H), 3.6–3.8 (m, 4H), 2.4–2.8 (m, 2H).[1]

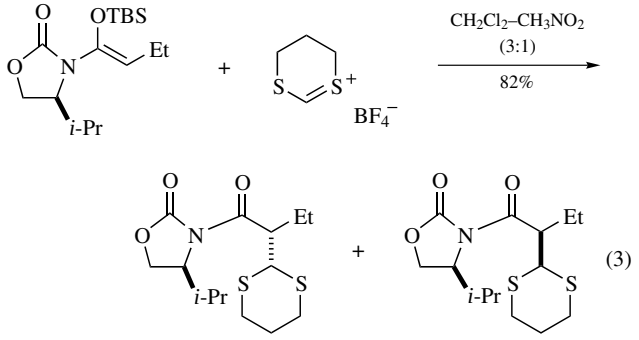
Preparative Methods: can be prepared by reaction of 1,3-dithiane with trityl tetrafluoroborate in dry CH_2Cl_2 at reflux (30 min), followed by solvent evaporation, trituration of the residue with cold Et_2O, collection of the solid by filtration, and drying in vacuo (92%).

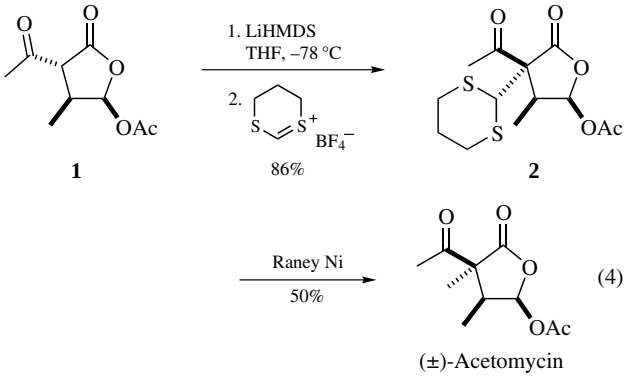
Handling, Storage, and Precaution: store at −20 °C under moisture-free conditions (where it is stable for several months).[1] Use in a fume hood.

Reactions. The title reagent is a powerful electrophile which reacts smoothly with silyl enol ethers.[2] The reaction produces a dithiane which is a masked version of β-keto aldehyde (eq 1). The reaction with a tetrasubstituted silyl enol ether provides a method for creating a quaternary carbon bearing a latent aldehyde function (eq 2).[2,3] Introduction of the dithiane group into a chiral nonracemic silyl enol ether occurs with high stereoselectivity and with the same absolute configuration seen with asymmetric enolate alkylation (eq 3).[4] Treatment of the lithium enolate of keto lactone **1** with 1,3-dithienium tetrafluoroborate gave dithiane **2** as a single isomer (eq 4).[5] Reductive desulfurization of **2** converted the dithiane substituent to a quaternary methyl group and furnished (±)-acetomycin. Silyl ketene acetals react with 1,3-dithienium tetrafluoroborate predominantly at the γ-carbon to afford γ-dithianyl-α,β-unsaturated esters in good yield and, in certain cases, with exclusive (*E*)-configuration.[6]

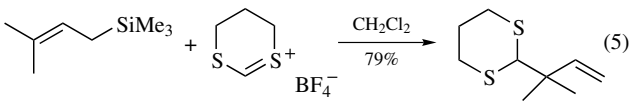


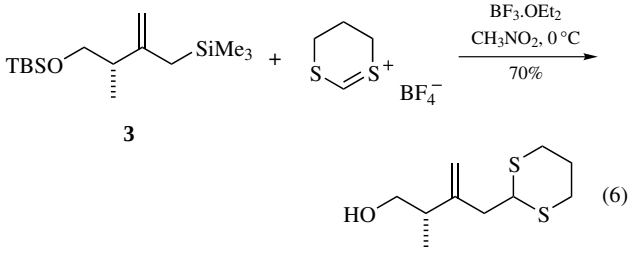




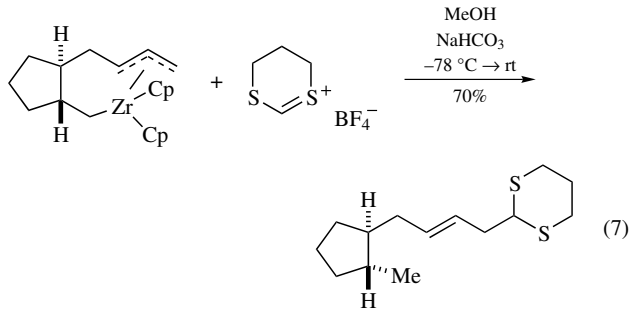


Allylsilanes are reactive towards 1,3-dithienium tetrafluoroborate. The intermediate β-silyl carbocation typically suffers elimination of the silyl cation to furnish a 2-allyl-1,3-dithiane (eq 5).[7] This protocol was employed to homologate allylsilane **3** to produce dithiane **4**, an intermediate in the synthesis of epiantillatoxin (eq 6).[8] A *tert*-butyldimethylsilyl ether used as a protecting group was cleaved from **3** during this reaction.

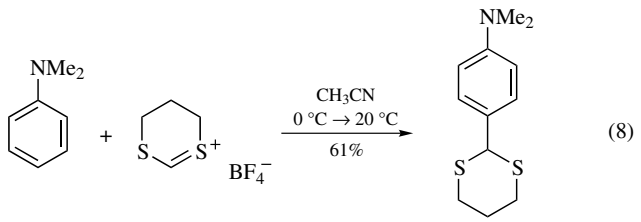




1,3-Dithienium tetrafluoroborate has been shown to react with a π-allylzirconium complex to give an allyldithiane (eq 7).[9] The reagent has also been used as an electrophile to introduce a carbon substituent into the *para* position of an activated benzene nucleus (eq 8).[10]

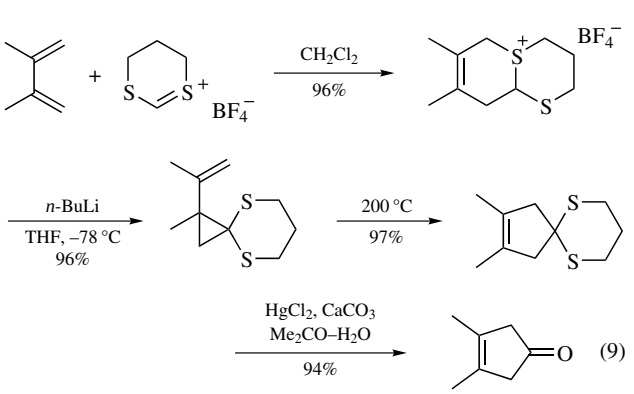


(7)



(8)

The reaction of 1,3-dithienum tetrafluoroborate with 1,3-dienes was among the first to be studied with this reagent and was found to follow a path which initially produced a bicyclic sulfonium salt (eq 9).[1,11] Deprotonation of this salt with *n*-butyllithium led to a vinylcyclopropane which rearranged under thermal conditions to a spirodithiane. Hydrolysis of the dithiane moiety gave a cyclopent-3-enone in an overall sequence that is formally equivalent to the addition of carbon monoxide across the terminal carbons of a 1,3-diene.



(9)

1. Corey, E. J.; Walinsky, S. W., *J. Am. Chem. Soc.* **1972**, *94*, 8932.
2. Paterson, I.; Price, L. G., *Tetrahedron Lett.* **1981**, *22*, 2829.
3. Liu, C.; Bao, G.; Burnell, D. J., *J. Chem. Soc., Perkin Trans. 1* **2001**, 2644.
4. Paterson, I.; Alexander, R. P., *Tetrahedron Lett.* **1985**, *26*, 5339.
5. Sprules, T. J.; Lavallée, J., *J. Org. Chem.* **1995**, *60*, 5041.
6. Paterson, I.; Price, L. G., *Tetrahedron Lett.* **1981**, *22*, 2833.
7. Westerlund, C., *Tetrahedron Lett.* **1982**, *23*, 4835.
8. White, J. D.; Hanselmann, R.; Wardrop, D. J., *J. Am. Chem. Soc.* **1999**, *121*, 1106.
9. Luker, T.; Whitby, R. J., *Tetrahedron Lett.* **1995**, *36*, 4109.
10. Stahl, I., *Chem. Ber.* **1987**, 135.
11. Mayr, H.; Henninger, J., *Eur. J. Org. Chem.* **1998**, 1919.

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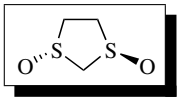
trans-1,3-Dithiolane 1,3-Dioxide[1]

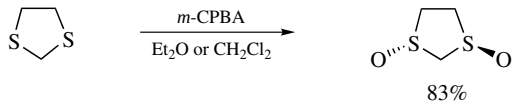


[79888-76-9] $C_3H_6O_2S_2$ (MW 138.21)
InChI = 1/C3H6O2S2/c4-6-1-2-7(5)3-6/h1-3H2/t6-,7-/s2
InChIKey = PFTBJUFGODPOCY-WZTWBHKBBF

(reagent used as a precursor of a chiral acyl anion equivalent)

Physical Data: mp 156–158 °C.
Solubility: poor solubility in etheral solvents, suspension in a 2:1 pyridine–THF mixture, soluble in acetone and dichloromethane.
Form Supplied in: white solid.
Analysis of Reagent Purity: mp, NMR.
Preparative Methods: the title reagent can be prepared by oxidation of 1,3-dithiolane (see below).
Purity: recrystallization from methanol, ethanol, isopropanol.

Synthesis. First obtained and described by Bennett and Statham in 1931,[2] racemic *trans*-1,3-dithiolane 1,3-dioxide can be conveniently prepared in a good yield (83%) by *m*-CPBA oxidation (eq 1) of 1,3-dithiolane in dichloromethane[3] or ether,[4] and with complete stereoselectivity (no *meso* adduct).



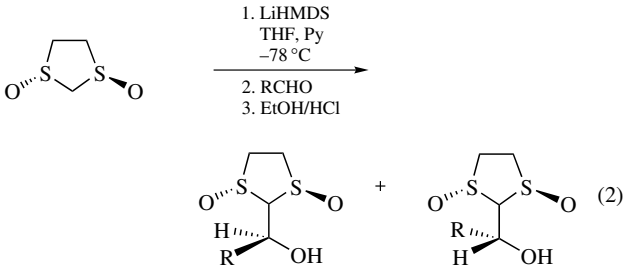
(1)

Enantiopure (*R*,*R*)-*trans*-1,3-dithiolane 1,3-dioxide has been reported.[5] It could be isolated after recrystallization of 54% enantioenriched product which was a very minor side-product of the monoxidation of 1,3-dithiolane by *Aspergillus foetidus*. So far, no viable pathway to the enantiopure derivatives has been devised.

1,2-Anionic Additions to Aldehydes. The pK_a of *trans*-1,3-dithiolane 1,3-dioxide has been determined by Bordwell and disclosed by Aggarwal to be 19.1,[4] a surprisingly low value compared to *trans*-1,3-dithiane 1,3-dioxide (24.9).[6] While the deprotonation of 1,3-dithiolane and 1,3-dithiolane 1-oxide leads to unstable carbanions that cleave, the anion of *trans*-1,3-dithiolane 1,3-dioxide has shown sufficient stability to undergo addition reactions with aldehydes. Moreover, because of the C_2-symmetry incorporated into a five-membered ring, its potential to serve as a chiral acyl anion equivalent has been tested.

For solubility reasons, a dual solvent system, i.e., THF/pyridine has to be used. Through variations in the metal counterion, reaction temperature, and the aldehyde used, it was shown that, contrary to *trans*-1,3-dithiane 1,3-dioxide, best reactivities were obtained at low temperatures (−78 °C) with a lithium ion. Even at that temperature with a sodium ion, as demonstrated by scrambling experiments with aldehydes, equilibration begins to occur with a slow reverse reaction. Upon heating, the equilibration erodes the good initial kinetic ratio and diminishes the yield. To completely circumvent this, the authors used 2.4 equiv of LiHMDS at −78°C. This results in the formation of a bis-sulfinyl

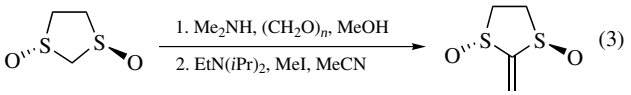
alkoxide dianion and renders the reaction irreversible. Under these optimal conditions, the best diastereoselectivities were still observed with aromatic and α,β-unsaturated aldehydes (eq 2). The authors attributed the greater propensity of the lithium ion of *trans*-1,3-dithiolane 1,3-dioxide to undergo reversible reaction to its high stability (*p*Ka 19.1). The stereoselectivity was rationalized by considering Zimmerman–Traxler transition states.[4]



(2)

R	Yield (%)	de (%)
Ph	90	92
crotyl	67	90
cyclohexyl	92	52
*t*Bu	53	62

Precursor of Dienophile. A sequence involving initial Mannich reaction followed by Hofmann elimination provides 2-methylene-1,3-dithiolane 1,3 dioxide (eq 3).[7] Alternative routes to the latter, including also an enantioselective access, have been reported along with its use in cycloaddition reactions.[7,8]



(3)

40%

Related Reagents. Several other chiral acyl anion equivalents have been published.[9] Comparison with 1,3-disulfur derived compounds is reported below. Benzaldehyde has been taken as the reference electrophile. The equivalents are of two kinds: mono- and dioxides. Generally, monoxides are slightly less efficient (85:15 ds)[10] or much more difficult to prepare and thus of scarce synthetic interest (100:0 ds).[11] Furthermore, they lead to additional problems because they lack C_2-symmetry. Dioxides are either cyclic or acyclic. Acyclic bis(sulfoxides) work also slightly less efficiently with benzaldehyde (90:10[12] to 95:5[13] ds), but slightly better with aliphatic aldehydes. The two reported cyclic dioxides (*trans*-1,3-dithiane 1,3-dioxide and *trans*-1,3-dithiolane 1,3-dioxide) are comparable and work equally well (>98:2 ds). Yet, there are some differences: *trans*-1,3-dithiolane 1,3-dioxide proceeds under kinetic control, while *trans*-1,3-dithiane 1,3-dioxide is best under thermodynamic conditions.[14] The latter also offers the advantage to be available in enantioenriched form.

1. Delouvrié, B.; Fensterbank, L.; Nájera, F.; Malacria, M., *Eur. J. Org. Chem.* **2002**, 3507.
2. Bennett, G. M.; Statham, F. S., *J. Chem. Soc.* **1931**, 1684.
3. Carey, F. A., Dailey, O. D., Jr; Fromuth, T. E., *Phosphorus Sulfur* **1981**, *10*, 163.
4. Aggarwal, V. K.; Schade, S.; Adams, H., *J. Org. Chem.* **1997**, *62*, 1139.
5. Auret, B. J.; Boyd, D. R.; Dunlop, R.; Drake, A. F., *J. Chem. Soc., Perkin Trans. 1* **1988**, 2827.
6. Aggarwal, V. K.; Davies, I. W.; Franklin, R.; Maddock, J.; Mahon, M. F.; Molloy, K. C., *J. Chem. Soc., Perkin Trans. 1* **1994**, 2363.
7. Aggarwal, V. K.; Gültekin, Z.; Grainger, R. S.; Adams, H.; Spargo, P. L., *J. Chem. Soc., Perkin Trans. 1* **1998**, 2771.
8. Aggarwal, V. K.; Grainger, R. S.; Adams, H.; Spargo, P. L., *J. Org. Chem.* **1998**, *63*, 3481.
9. Gaul, C.; Schärer, K.; Seebach, D., *J. Org. Chem.* **2001**, *66*, 3059, and references cited therein.
10. Colombo, L.; Gennari, C.; Scolastico, C.; Guanti, G.; Narisano, E., *J. Chem. Soc., Chem. Commun.* **1979**, 591.
11. Delogu, G.; De Lucchi, O.; Maglioli, P.; Valle, G., *J. Org. Chem.* **1991**, *56*, 4467.
12. Solladié, G.; Colobert, F.; Ruiz, P.; Hamdouchi, C.; Carreño, M. C.; Garcìa Ruano, J. L., *Tetrahedron Lett.* **1991**, *30*, 3695.
13. Delouvrié, B.; Nájera, F.; Fensterbank, L.; Malacria, M., *J. Organomet. Chem.* **2002**, *643–644*, 130.
14. Aggarwal, V. A.; Franklin, R.; Maddock, J.; Evans, G. R.; Thomas, A.; Mahon, M. F.; Molloy, K. C.; Rice, M. J., *J. Org. Chem.* **1995**, *60*, 2174.

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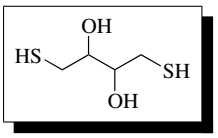
1,4-Dithiothreitol[1]



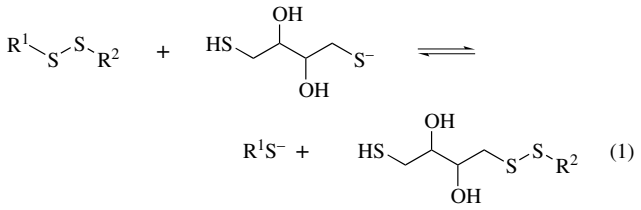
[27565-41-9] $C_4H_{10}O_2S_2$ (MW 154.28)
InChI = 1/C4H10O2S2/c5-3(1-7)4(6)2-8/h3-8H,1-2H2/t3-,4-/s2
InChIKey = VHJLVAABSRFDPM-SEFKMRKOBY

(reducing agent for disulfides;[1,2] protection of thiols and proteins containing free SH groups from air oxidation[3])

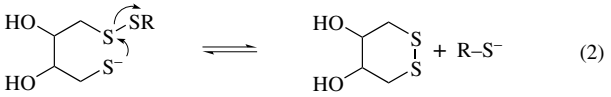
Alternative Name: DTT; *threo*-2,3-dihydroxybutane-1,4-dithiol.
Physical Data: mp 42–44 °C (racemate); redox potential −0.33 V, pH 7, varying −0.06 V per pH unit; p*K* 9.2 and 10.1.
Solubility: very sol water, alcohols.
Form Supplied in: white solid; widely available; normally supplied as the racemate, but chiral 1,4-dithio-L-threitol [*16096-97-2*],[4] mp 49–51 °C, is also available. The *erythro* isomer (1,4-dithioerythritol, DTE, [*6892-68-8*], mp 82–84 °C)[1] has redox properties similar to the *threo* isomer ($E^{\circ\prime}$ is more positive by 0.004 V)[5] and is also available. The oxidized cyclic form (*trans*-1,2-dithiane-4,5-diol [*14193-38-5*], mp 130–132 °C)[1] is available; it has a UV spectrum (λ_{max} 283 nm; ε = 273). DTT and DTE are colorless above 260 nm, but both reduced and oxidized forms absorb below 240 nm.
Analysis of Reagent Purity: the presence of monothiols can be detected by addition of arsenite (which forms a tight tridentate complex with DTT),[6] followed by addition of 5,5′-dithiobis-(2-nitrobenzoate).[7] Total thiol content is determined by omitting arsenite.

Handling, Storage, and Precautions: solid material should be stored under refrigeration in a closed bottle. Solutions will slowly oxidize in the presence of air to the cyclic disulfide, which is inert. The concentration of reduced material can be determined by assay with 5,5′-dithiobis(2-nitrobenzoate).[8]

Reduction of Disulfides. DTT and DTE are the reagents of choice for reducing disulfide bonds, and protecting thiols and the thiol groups on proteins from air oxidation to disulfides.[1–3] DTT also reduces diselenides.[9] The equilibrium constant for reduction of the disulfide of glutathione by DTT is 210 M.[10] DTT undergoes disulfide interchange to liberate the thiol with the lowest pK (eq 1). The mixed disulfide then cyclizes rapidly, releasing the other monothiol (eq 2).



(1)



(2)

The high equilibrium constant for this cyclization reaction produces the low redox potential for DTT. The hydroxy groups at C-2 and C-3 convey water solubility and reduce the stench (the solid has an odor, but only at very close range). Since the active form for disulfide interchange is the thiolate anion, these reactions go faster at higher pH. With the first p*K* at 9.2, however, there is sufficient thiolate even at pH 7 to give a reasonable rate.

The rates of reduction of disulfides by DTT show a normal dependence on the p*K* of the thiol being liberated,[11] and this fact has been used to determine the p*K*'s of SH groups on proteins. For example, the p*K* of the active site cysteine in papain was 4.1 at pH 6 and 8.4 at pH 9, with the change resulting from a group titrating with a p*K* of 7.5.[11b] The equation used in this work was: $\log k = 7.03 + 0.5\ \mathrm{p}K_{\mathrm{nuc}} - 0.27\ \mathrm{p}K_{\mathrm{c}} - 0.73\ \mathrm{p}K_{1\mathrm{g}}$, where k is the rate constant in $M^{-1}\ min^{-1}$ for reaction of the monoanion of DTT with the disulfide, and the subscripts nuc, c, and 1g refer to DTT, the center sulfur in the transition state, and the leaving thiol on the protein.

A series of other dithiols have been prepared as potential reducing agents, but none of them that are water soluble have lower redox potentials than DTT.[10,12] Two that have lower p*K*'s (7.6–7.8) and thus react faster at neutral pH have higher redox potentials of −0.27 V at pH 7 and are less effective reducing agents than DTT.[13] So far, none of these is commercially available.

Reagent for Studies of Protein Folding. DTT and its oxidized form have found use in studying disulfide interchange reactions during protein folding and unfolding.[14] Mixtures of these provide a redox buffer that can be adjusted to match the redox potential of individual disulfide bonds.

Other Properties and Problems. The low redox potential of dithiothreitol interferes with its use in the presence of certain reagents. While it gives full color yield in reactions with aromatic disulfides such as 5,5′-dithiobis(2-nitrobenzoate)[8] or 2,2′- or 4,4′-dipyridyl disulfide,[15] it gives only 4% the expected color in the nitroprusside assay for thiols,[1,16] presumably because it reduces the iron. It reduces Cr^{III} or Co^{III}, so inert complexes of nucleotides with these metal ions cannot be used in its presence. Dithiothreitol also undergoes transesterification with thioesters of coenzyme A.[17]

DTT and DTE chelate heavy metal ions tightly, which can be helpful at times, but deleterious with autooxidizable ions such as Fe^{II}. While they oxidize only slowly in air in the absence of heavy metal ions, DTT and DTE are readily oxidized in air in the presence of Fe^{II}, so solutions containing Fe^{II} and DTT must be kept anaerobic.[18]

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1. Cleland, W. W., *Biochemistry* **1964**, *3*, 480.
2. Jocelyn, P. C., *Methods Enzymol.* **1987**, *143*, 246.
3. Konigsberg, W., *Methods Enzymol.* **1972**, *25*, 185.
4. Carmack, M.; Kelley, C. J., *J. Org. Chem.* **1968**, *33*, 2171.
5. Szajewski, R. P.; Whitesides, G. M., *J. Am. Chem. Soc.* **1980**, *102*, 2011.
6. Cruse, W. B. T.; James, M. N. G., *Acta Crystallogr. B* **1972**, *28*, 1325.
7. Zahler, W. L.; Cleland, W. W., *J. Biol. Chem.* **1968**, *243*, 716.
8. Ellman, G. L., *Arch. Biochem. Biophys.* **1959**, *82*, 70.
9. Gunther, W. H. H., *J. Org. Chem.* **1967**, *32*, 3931.
10. Lees, W. J.; Whitesides, G. M., *J. Org. Chem.* **1993**, *58*, 642.
11. (a) Whitesides, G. M.; Lilburn, J. E.; Szajewski, R. P., *J. Org. Chem.* **1977**, *42*, 332. (b) Shaked, Z.; Szajewski, R. P.; Whitesides, G. M., *Biochemistry* **1980**, *19*, 4156.
12. Houk, J.; Whitesides, G. M., *J. Am. Chem. Soc.* **1987**, *109*, 6825. The values in this paper are in error and have been correctly given in reference 10.
13. Singh, R.; Whitesides, G. M., *J. Org. Chem.* **1991**, *56*, 2332. Lees, W. J.; Singh, R.; Whitesides, G. M., *J. Org. Chem.* **1991**, *56*, 7328.
14. Creighton, T. E., *Methods Enzymol.* **1986**, *131*, 83.
15. Grassetti, D. R.; Murray, J. F., Jr., *Arch. Biochem. Biophys.* **1967**, *119*, 41.
16. Grunert, R. R.; Phillips, P. H., *Arch. Biochem. Biophys.* **1951**, *30*, 217.
17. Stokes, G. B.; Stumpf, P. K., *Arch. Biochem. Biophys.* **1974**, *162*, 638.
18. Lambeth, D. O.; Ericson, G. R.; Yorek, M. A.; Ray, P. D., *Biochim. Biophys. Acta* **1982**, *719*, 501.

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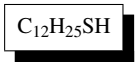
tert-Dodecanethiol



[25103-58-6] $C_{12}H_{26}S$ (MW 202.40)

InChI = 1/C12H26S/c1-10(2,3)8-12(7,13)9-11(4,5)6/h13H,8-9H2,1-7H3

InChIKey = CXUHLUIXDGOURI-UHFFFAOYAF

(mainly used as hydrogen-transfer reagent in many synthetic applications)

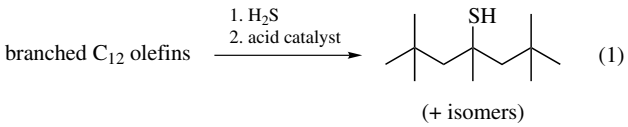
Alternate Names: 2,2,4,6,6-pentamethyl-4-heptanethiol (major, representative component), *tert*-dodecylmercaptan, *tert*-laurylmercaptan, TDM, *t*-DDM, Sulfole® 120.

Physical Data: mp ca. −45 °C, bp 227–248 °C (760 mm Hg), d 0.86 g cm^{-3} (20 °C).

Solubility: sol most organic solvents; water solubility: 0.25 mg dm^{-3} (20 °C).

Form Supplied in: colorless to pale-yellow liquid; mercaptan odor; widely commercially available; for impurities, see next section.

Preparative Methods: : *tert*-dodecanethiol is generally prepared by homogeneous or heterogeneous acid-catalyzed addition of hydrogen sulfide to branched C_{12} olefins.[1] Typical starting materials are propylene tetramer and butene or isobutene trimers. Both feedstocks contain highly branched C_{12} olefins (mixture of isomers) as major components, accompanied by minor percentages of C_{10}–C_{15} alkenes: the resulting thiol is therefore a mixture of isomeric tertiary dodecanethiols associated with minor amounts of other longer- and shorter-chain alkanethiols. The CAS number *[25103-58-6]* refers to that mixture of isomers, whose best-supported representative structure is 2,2,4,6,6-pentamethyl-4-heptanethiol (eq 1). The differences in properties that might exist between the various isomers is not considered to be important. Common catalysts for the synthesis can be protic acids (e.g., hydrofluoric, methanesulfonic, and carbonic acids), Lewis acids (e.g., boron trifluoride, aluminum chloride, tin(IV) chloride, and complexes thereof), and heterogeneous catalysts such as clays, resins (e.g., Amberlyst® 15), zeolites, silicoaluminates, and modified titania, zirconia, and alumina.

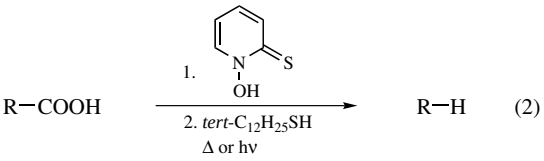


Purification: the commercially available product (mixture of isomers also containing minor quantities of other C_{10}–C_{15} alkane thiols) is generally used without further purification as being highly satisfactory for most purposes.

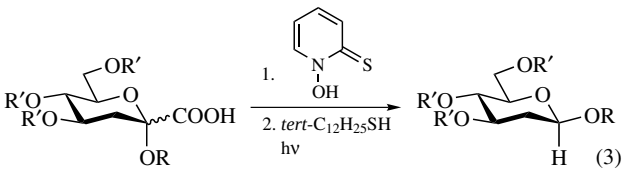
Handling, Storage, and Precautions: like most thiols, this compound has a tendency to undergo oxidation on exposure to air, but it remains essentially unchanged when stored at rt in the absence of air. Although much less malodorous than other alkanethiols, this compound has a typical mercaptan odor and should be used in a well-ventilated fume hood. Incompatible with strong bases and oxidizing agents. *tert*-Dodecanethiol has a low order of acute toxicity to mammals, the oral LD_{50} values in rats being included in the range 2150–15,000 mg kg^{-1}.

Hydrogen-transfer Reagent in Radical Reactions. Thiols, in particular tertiary mercaptans such as *tert*-butanethiol[2] and triethylmethanethiol,[3] have been widely used in radical reactions to trap radical intermediates by hydrogen atom transfer. *tert*-Dodecanethiol is a valid substitute for those mercaptans, since it is cheap, relatively odorless compared to the other alkanethiols, and generally equally efficient with respect to the hydrogen donor properties.

A typical procedure that employs this thiol as a hydrogen donor is the Barton reductive decarboxylation. These reactions make use of the Barton *O*-acyl thiohydroxamate chemistry, entailing condensation of a carboxylic acid, or the corresponding chloride, with *N*-hydroxypyridine-2-thione, or its sodium salt, followed by thermal or photochemical decomposition of the resulting thiohydroxamate. The presence of *tert*-dodecanethiol ensures that the alkyl radical arising from decomposition of the thiohydroxamate is quenched by hydrogen transfer instead of being trapped by the thiohydroxamate itself (eq 2).

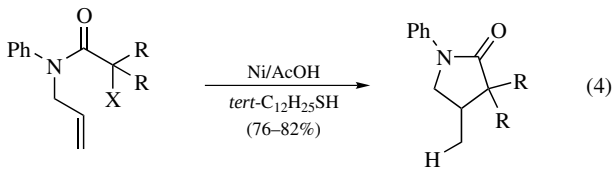


This procedure was first successfully employed in highly diastereoselective radical hydrogen transfer reactions leading to β-glycosides (eq 3).[4]



36–75%, α:β ratio >1:8

Analogous reactions based on the same protocol were used in the stereocontrolled enantiospecific synthesis of anticapsin,[5] in the synthesis of D-xylose from noncarbohydrate sources,[6] and in the synthesis of an intermediate for a furopyridinone antibiotic.[7] This latter synthesis employed a novel reagent (*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate)[8] for the preparation of hindered Barton esters. Usual Barton esters can be replaced by hydroxamates from *N*-hydroxy-4-methylthiazolinethione, as in a key step of the synthesis of (±)-matrine,[9] or peresters, as in the preparation of 3-decarboxy squalestatins.[10] The H-donor properties of *tert*-dodecanethiol were also exploited for trapping the alkyl radicals generated in cyclizations of α-haloamides to γ-lactams triggered by nickel powder/acetic acid (eq 4).[11] In the absence of the thiol, halomethylated lactams deriving from an alternative halogen-atom-transfer process were obtained.

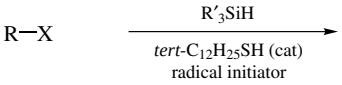


Finally, the hydrogen transfer ability of *tert*-dodecanethiol makes this compound a good reagent for controlling the chain length in many radical reactions. Therefore, this thiol finds extensive use in particular as a chain-transfer reagent (or "modifier") to control molecular weight distribution in emulsion radical polymerizations (especially in production of styrene–butadiene and acrylonitrile–butadiene synthetic rubbers, but also, to a minor extent, for polystyrene and ABS plastics).[12] The chain-length control occurs by hydrogen transfer from the thiol to the growing

polymer radical and is strictly related to the thiol concentration (typically 0.01–2% of the polymerization mixture).

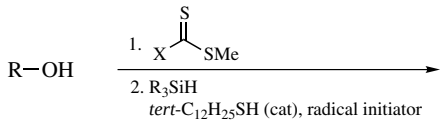
Reagent for Polarity Reversal Catalysis in Radical Reactions. Polarity reversal catalysis (PRC)[13] has been established by Roberts in free-radical chemistry as an efficient alternative to the use of stannanes (e.g., tri-*n*-butylstannane) and their associated toxicity and purification problems. Silyl radicals can be a valid alternative to tin radicals for one of the most common radical reactions, that is, radical dehalogenation, but silanes, contrary to stannanes, cannot sustain an effective radical chain reaction, due to the stronger Si–H bond.

This problem has been circumvented by carrying out the reactions in the presence of catalytic amounts of a thiol. Because of polar effects, thiols are very good hydrogen donors towards the nucleophilic alkyl radicals generated by silyl-radical-mediated halogen abstraction from alkyl halides; the resulting electrophilic sulfanyl radicals are in turn able to abstract the nucleophilic hydrogen of the silane (e.g., triethylsilane) to regenerate the thiol and a new silyl radical that sustains the chain. *tert*-Dodecanethiol can be effectively used as the thiol catalyst in such (and related) processes (eq 5).

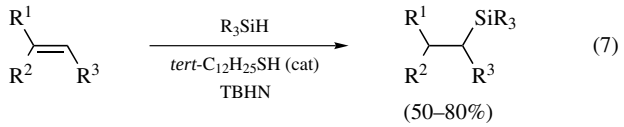


(5)

Examples of application of the *tert*-dodecanethiol/silane couple include typical reductive dehalogenations,[14] but also Barton-McCombie deoxygenations of alcohols, through conversion of the latter into xanthate esters (eq 6),[15] hydrosilylations of alkenes (eq 7),[16] and preparation of silanethiols.[17] The thiol can also be used as a polarity reversal catalyst in conjunction with tris(trimethylsilyl)silane[18] and hexabutyldistannane/malonic acid.[19]



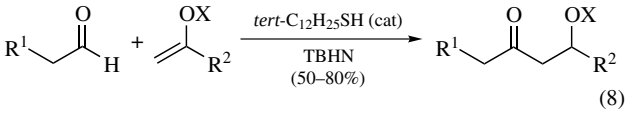
(6)



(7)

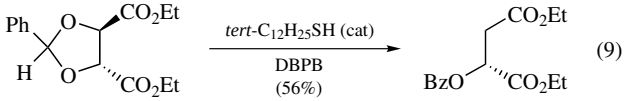
[TBHN = *tert*-butyl hyponitrite (rad. initiator)]

Interestingly, the polarity reversal catalysis concept can be applied to other thiol/RH couples, provided that the polar effects between the counterparts are able to sustain the radical chain. The protocol has therefore been extended to aldehydes and acetals (or alkyl ethers), whose hydrogen atoms have the same nucleophilic characteristics (and comparable BDEs as well) of the hydrogen atom of silanes. The sulfanyl radicals derived from *tert*-dodecanethiol have hence been proven to be able to abstract the aldehydic hydrogen of aliphatic aldehydes to give acyl radicals, which are in turn capable of adding to enol esters and silyl enol ethers to give a homolytic disconnection for aldols (eq 8).[20] The acyl radicals obtained from alkenals can also give cyclization onto their olefinic moieties to give cyclic ketones.[21]



(8)

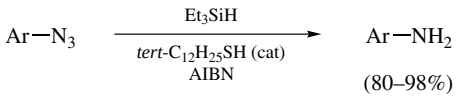
Analogously, PRC has been exploited to selectively epimerize carbon centers of the type $R^1R^2C(H)OR^3$, for example, to convert a readily available carbohydrate-based diastereoisomer into a rarer one,[22] and in ring opening of acetals to benzoate esters:[23] (eq 9) shows the conversion of a derivative of natural (*R*,*R*)-tartartic acid into that of unnatural (*R*)-malic acid.



(9)

[DBPB = 2,2-di-*tert*-butylperoxybutane (rad. initiator)]

Very recently, a PRC radical protocol has also been used to convert aromatic azides into amines (eq 10).[24]



(10)

Miscellaneous. Addition of *tert*-dodecanethiol to isonitriles can result in sulfur atom transfer to the isonitrile with formation of an isothiocyanate.[25] The thiol can be transformed with sodium nitrite/sulfuric acid into the corresponding thionitrite (*S*-nitrosothiol), which can be a convenient nitric oxide transfer agent from sulfur to primary and secondary carbon atoms through radical decarboxylative nitrosation reactions.[26] Thiols (both soluble and solid supported ones) and *tert*-dodecanethiol among these[27] have been recently showed to be more efficient reagents than piperidine, as a dibenzofulvene scavenger, for deprotection of *N*-Fmoc amines.[28] Finally, *tert*-dodecanethiol can be used to protect gold nanoparticles, which are then employed to prepare new organic/inorganic self-assembled nanomaterials.[29]

Related Reagents. Thiophenol; Benzeneselenol; Triisopropylsilanethiol.

1. Roy, K.-M. *Thiols and Organic Sulfides in Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2005. All of the reported syntheses of *tert*-dodecanethiol are included in patents or non-English-language journals.
2. Barton, D. H. R.; Crich, D.; Kretzshmar, G., *J. Chem. Soc., Perkin Trans. 1* **1986**, 39. See also: Crich, D.; Quintero, L., *Chem. Rev.* **1989**, *89*, 1413, and refs. therein.
3. Bloodworth, A. J.; Crich, D.; Melvin, T., *J. Chem. Soc., Chem. Commun.* **1987**, 786.
4. (a) Crich, D.; Ritchie, T. J., *J. Chem. Soc., Chem. Commun.* **1988**, 1461. (b) Crich, D.; Ritchie, T. J., *J. Chem. Soc., Perkin Trans. 1* **1990**, 945. (c) Crich, D.; Lim, L. B., *J. Chem. Soc., Chem. Commun.* **1991**, 2205. (d) Crich, D.; Lim, L. B., *J. Chem. Soc., Perkin Trans. 1* **1991**, 2209. (e) Crich, D.; Lim, L. B., *Tetrahedron Lett.* **1991**, *32*, 2565.
5. Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B., *Tetrahedron* **1995**, *51*, 5193.
6. Banwell, M. G.; De Savi, C.; Hockless, D. C. R.; Pallich, S.; Watson, K. G., *Synlett* **1999**, 885.

7. Clive, D. L. J.; Huang, X., *Tetrahedron* **2002**, *58*, 10243.
8. Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K., *J. Org. Chem.* **1998**, *63*, 5732.
9. Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z., *Angew Chem. Int. Ed.* **1998**, *37*, 1128.
10. Chan, C.; Inglis, G. G. A.; Procopiou, P. A.; Ross, B. C.; Srikantha, A. R. P.; Watson, N. S., *Tetrahedron Lett.* **1993**, *34*, 6143.
11. Boivin, J.; Yousfi, M.; Zard, S. Z., *Tetrahedron Lett.* **1994**, *35*, 5629.
12. For some representative examples of the extensive literature concerning the use of *tert*-dodecanethiol in polymerizations, see: (a) Verdurmen, E. M.; Geurts, J. M.; Verstegen, J. M.; Maxwell, I. A.; German, A. L., *Macromolecules* **1993**, *26*, 6289. (b) Salazar, A.; Gugliotta, L. M.; Vega, J. R.; Meira, G. R., *Ind. Eng. Chem. Res.* **1998**, *37*, 3582. (c) Manders, B. G.; Morrison, B. R.; Klostermann, R., *Macromol. Symposia* **2000**, *155*, 53.
13. (a) Parsons, A. F. *An Introduction to Free Radical Chemistry*; Blackwell Science: Oxford, 2000; p 110. (b) Roberts, B., *Chem. Soc. Rev.* **1999**, *28*, 25.
14. (a) Allen, R. P.; Roberts, B. P.; Willis, C., *J. Chem. Soc., Chem. Commun.* **1989**, 1378. (b) Cai, Y.; Roberts, B. P., *J. Chem. Soc., Perkin Trans. 2* **2002**, 1858.
15. (a) Kirwan, J. N.; Roberts, B. P.; Willis, C., *Tetrahedron Lett.* **1990**, *31*, 5093. (b) Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R., *J. Chem. Soc,. Perkin Trans. 1* **1991**, 103.
16. (a) Smadja, W.; Zahouily, M.; Journet, M.; Malacria, M., *Tetrahedron Lett.* **1991**, *32*, 3683. (b) Dang, H.-S.; Roberts, B. P., *Tetrahedron Lett.* **1995**, *36*, 2875. (c) Haque, M. B.; Roberts, B. P., *Tetrahedron Lett.* **1996**, *37*, 9123.
17. Cai, Y.; Roberts, B. P., *Tetrahedron Lett.* **2001**, *42*, 4581.
18. Chatgilialoglu, C., *Helv. Chim. Acta* **2006**, *89*, 2387.
19. Kim, K.-M.; Roberts, B. P., *J. Chem. Res. (S)* **1998**, 132.
20. Dang, H.-S.; Roberts, B. P., *J. Chem. Soc., Chem. Commun.* **1996**, 2201.
21. Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.-I.; Tomioka, K., *J. Org. Chem.* **2005**, *70*, 681.
22. (a) Dang, H.-S.; Roberts, B. P., *Tetrahedron Lett.* **1999**, *40*, 4271. (b) Dang, H.-S.; Roberts, B. P.; Tocher, D. A., *J. Chem. Soc., Perkin Trans. 1* **2001**, 2452.
23. (a) Roberts, B. P.; Smits, T. M., *Tetrahedron Lett.* **2001**, *42*, 137. (b) Roberts, B. P.; Smits, T. M., *Tetrahedron Lett.* **2001**, *42*, 3663.
24. Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G., *J. Org. Chem.* **2006**, *71*, 5822.
25. Bachi, M. D.; Balanov, A.; Bar-Ner, N., *J. Org. Chem.* **1994**, *59*, 7752.
26. Girard, P.; Guillot, N.; Motherwell, W. B.; Hay-Motherwell, R. S.; Potier, P., *Tetrahedron* **1999**, *55*, 3573.
27. Sakamoto, K.; Nakahara, Y.; Ito, Y., *Tetrahedron Lett.* **2002**, *43*, 1515.
28. Sheppeck, J. E., II; Kar, H.; Hong, H., *Tetrahedron Lett.* **2000**, *41*, 5329.
29. Araki, K.; Mizuguchi, E.; Tanaka, H.; Ogawa, T., *J. Nanosci. Nanotechnol.* **2006**, *6*, 708.

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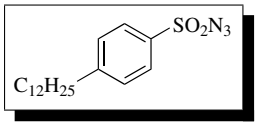
p-Dodecylbenzenesulfonyl Azide



[79791-38-1] $C_{18}H_{29}N_3O_2S$ (MW 351.57)

InChI = 1/C18H29N3O2S/c1-2-3-4-5-6-7-8-9-10-11-12-17-13-15-18(16-14-17)24(22,23)21-20-19/h13-16H,2-12H2,1H3

InChIKey = DYEGEQTYEIHCSO-UHFFFAOYAM

[119652-78-7]

InChI = 1/C18H29N3O2S/c1-2-3-4-5-6-7-8-9-10-11-12-17-13-15-18(16-14-17)24(22,23)21-20-19/h13-16H,2-12H2,1H3

InChIKey = DYEGEQTYEIHCSO-UHFFFAOYAM

(diazo-transfer reagent for activated methylene groups[1])

Alternate Name: *p*-DBSA.

Physical Data: liquid mixture of isomers without precise mp or bp.

Solubility: sol pentane, acetone, and most organic solvents.

Form Supplied in: viscous liquid.

Analysis of Reagent Purity: elemental analysis (C, H, N, S) and HPLC.

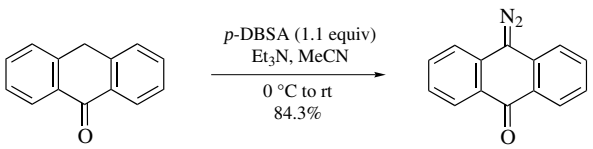
Preparative Method: prepared by addition of granular sodium azide (1.3 equiv) to a mixture of isomeric sulfonyl chlorides (from a commercial mixture of isomers of *p*-dodecylbenzenesulfonic acid) in acetone solution.[1]

Purification: elution through short column containing silica gel G with methylene chloride–hexane (1:4) as eluant.[1]

Handling, Storage, and Precautions: is the safest of the usual arenesulfonyl azides (tosyl azide, etc.) employed in diazo-transfer processes;[1] appropriate care should be taken, as with all azides. Use in a fume hood.

Reagent for Diazo-function Transfer. The title reagent has been called a safer diazo-transfer reagent, and is a mixture of 12 or more isomeric *p*-dodecylbenzenesulfonyl azides, ranging by HPLC from 24% to 1% in area and giving essentially a single spot by TLC.[1]

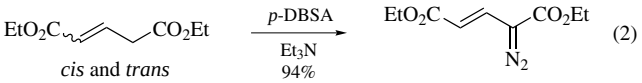
The title reagent has been shown to be very useful for the synthesis of various crystalline diazocarbonyl compounds such as diazobarbituric and diazoisopropylidenemalonic acids,[1] derivatives and homologs of diazoacetoacetic acid,[1,2] and 9-diazoanthrone (eq 1).[1]



(1)

Formation of noncrystalline byproduct dodecylsulfonamides facilitates the workup procedure and isolation of the target crystalline diazo compounds from the reaction mixture.[1]

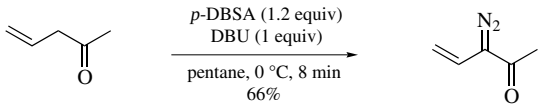
Vinyldiazomethanes containing two electron-withdrawing groups are readily available using *p*-DBSA in the presence of triethylamine (eq 2).[3]



(2)

The process seems to be nonstereospecific. From a mixture of diethyl *cis*- and *trans*-glutaconates, exclusively the *trans*-diazo compound was isolated in high yield, indicating that equilibration occurs under the reaction conditions.[3]

The reagent is also effective in the case of allyl methyl ketone, which has a less acidic methylene group than the previous substrate (eq 3).[4]



(3)

The reaction is complete in a few minutes but a stronger base, 1,8-diazabicyclo[5.4.0]undec-7-ene, is required for initial anion formation.

1. Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W., *Synth. Commun.* **1981**, *11*, 947.
2. (a) Davies, H. M. L.; Crisco, L. Van T., *Tetrahedron Lett.* **1987**, *28*, 371. (b) Doecke, Ch. W. Eur. Patent 345 999 (*Chem. Abstr.* **1990**, *113*, 23 522n). (c) Hughes, D. L. Eur. Patent 409 331 (*Chem. Abstr.* **1991**, *115*, 9051t). (d) Nagao, Y.; Kumagai, T.; Tamai, S.; Kuramoto, Y.; Shimizu, H.; Nagase, Y. Jpn. Patent 63 170 377 [88 170 377] (*Chem. Abstr.* **1989**, *110*, 154 039w).
3. Davies, H. M. L.; Clark, D. M.; Smith, T. K., *Tetrahedron Lett.* **1985**, *26*, 5659.
4. Davies, H. M. L.; Saikali, E.; Young, W. B., *J. Org. Chem.* **1991**, *56*, 5696.

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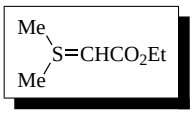
E

Ethyl (Dimethylsulfuranylidene)acetate



[7380-81-6] $C_6H_{12}O_2S$ (MW 148.25)
InChI = 1/C6H12O2S/c1-4-8-6(7)5-9(2)3/h5H,4H2,1-3H3
InChIKey = HOKIBTXDUCLZQR-UHFFFAOYAT

(stabilized sulfonium ylide reagent capable of reacting with a variety of electrophiles to produce substituted cyclopropanes, epoxides, enamines, and stabilized ylides, as well as other products[1])

Alternate Name: EDSA.
Physical Data: *d* 1.52 g cm^{-3}.
Solubility: toluene, benzene, CH_2Cl_2, acetone, THF, EtOH
Form Supplied in: not available commercially.
Preparative Method: synthesized in two simple steps (85% overall yield). An equimolar combination of ethyl bromoacetate and dimethyl sulfide is stirred in acetone at rt for three days, after which the precipitated sulfonium salt is isolated by filtration. The salt is then converted to the ylide by treatment with K_2CO_3/NaOH in $CHCl_3$/water.[1b]
Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H), 3.9 (q, 2H), 2.7–2.8 (br s, 7H).
Handling, Storage, and Precautions: although the reagent is subject to moisture-induced and thermal decomposition, no report of hazard has been found. The presence of water gives rise to ester hydrolysis and quenching of the ylide to form the zwitterionic sulfonium carboxylate $Me_2S^+CH_2CO_2^-$. Significant instability has also been noted at slightly elevated temperatures (35% decomposition at 80 °C in 3 h). Successful storage (several weeks) can be accomplished at −10 °C under anhydrous conditions.[1b]

Original Commentary

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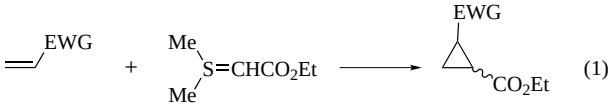
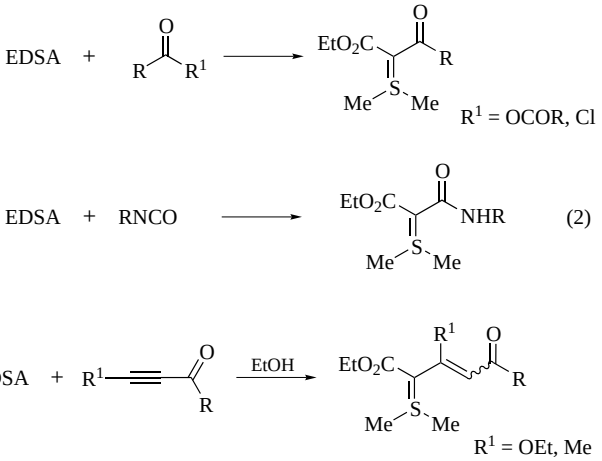
Cyclopropanations. A variety of electron-deficient alkenes react with this reagent in aprotic solvents to produce good yields of ethoxycarbonyl-substituted cyclopropanes (eq 1). EtOH and presumably other protic solvents allow alternative reaction pathways which seem to be dependent on proton transfer.[1c] The mechanism can be thought of as 1,4-addition followed by intramolecular ring closure with loss of dimethyl sulfide. In general, the reaction succeeds for double bonds activated by one or two strong electron-withdrawing groups (EWG) which may include CHO, COR, CO_2R, CN, and CF_3 (Table 1).[1b,2–8] The reaction is stereoselective in favor of the *trans* product but in certain cases the selectivity is only marginal.

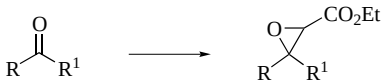


(1)

Stabilized Sulfur Ylides. Acid chlorides, anhydrides, and isocyanates acylate EDSA to generate good yields of stabilized sulfur ylides. In addition, alkynes conjugated with either ketones or esters react in a similar fashion (eq 2).[1e]



Epoxidations. In contrast to dimethylsulfonium methylide,[9] EDSA usually does not react with aldehydes or ketones in a 1,2-sense to generate epoxides. However, under certain conditions,[1e] electron-deficient carbonyls do undergo this reaction. Thus EDSA can be considered an alternative (albeit of limited scope) to α-haloacetic acid esters in the Darzens condensation (eq 3).[10]



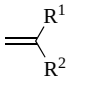
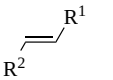
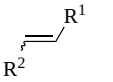
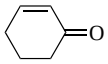
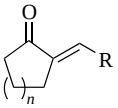
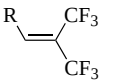
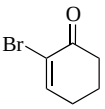
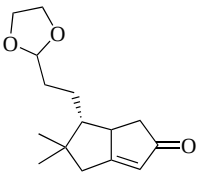
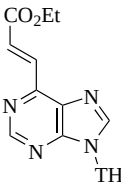
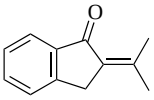
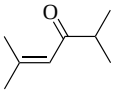
(3)

R = Me, R^1 = COMe, 50%
R = Ph, R^1 = COPh, 92%
R = Me, R^1 = CO_2Et, 42%
R = H, R^1 = CCl_3, 22%

Interestingly, the carboxylate salt of EDSA has been reported to epoxidize unactivated ketones.[11]

Alternative Reagents. While ethyl diazoacetate[12] also reacts with alkenes to provide good yields of ethoxycarbonyl substituted cyclopropanes, it can be differentiated from EDSA in two ways. In the first place, EDSA, requiring an electron deficient double bond, can be considered more selective. Secondly, in large scale reactions, ethyl diazoacetate carries a risk of explosion which EDSA does not have. Ethyl chloroacetate (or methyl chloroacetate) under basic conditions accomplishes the same transformation as EDSA.[13]

Table 1 Cyclopropanation reaction with EDSA

Structure	Substitution	Yield (%)
	R^1 = CHO, R^2 = H	63[1b]
	R^1 = CO_2Et, R^2 = H	84
	R^1 = COMe, R^2 = H	87
	R^1 = CHO, R^2 = Me	86
	R^1 = CO_2Me, R^2 = Me	69
	R^1 = CO_2Me, R^2 = CH_2CO_2Me	89
	R^1 = CHO, R^2 = Me	50[1b]
	R^1 = CO_2Et, R^2 = Me	79
	(*E*)R^1 = CO_2Et, R^2 = CO_2Et	91[1b]
	(*Z*)R^1 = CO_2Et, R^2 = CO_2Et	79
		71[1b]
		75[1b]
	*n* = 3, R = Ph	–[2]
	n = 3, R = *i*-Pr	–
	n = 2, R = Ph	–
	n = 2, R = 2-furanyl	–
	n = 3, R = 2-furanyl	–
	R = CH=CCl_2	42[3]
	R = CH(Cl)-*i*-Pr	75
	R = $CH(OEt)_2$	84
	R = CH(OCOMe)-*i*-Pr	87
		84[4]
	mixture of (*E*) and (*Z*)	72[8]
	mixture of (*E*) and (*Z*)	90[5]
		100[6]
		50[7]

First Update

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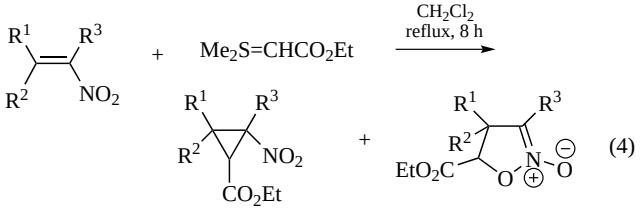
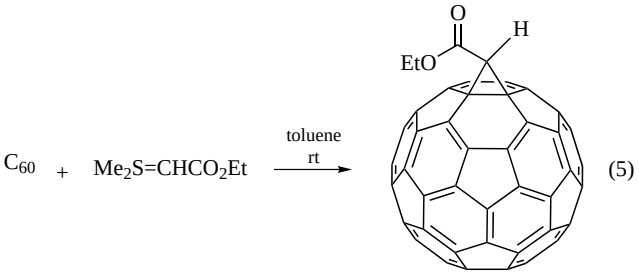
Cyclopropanations. More recent examples on nonchiral substrates include the cyclopropanation reactions of nitroalkenes (eq 4),[15] [60]fullerene (C_{60})[16] (eq 5), and [70]fullerene (C_{70}).[17] The first mentioned reactions (eq 4) give either exclusively nitrocyclopropanes or mixtures of nitrocyclopropanes and isoxazoline *N*-oxides in which isoxazolines are the major products. The latter product mixtures are favored when R^3 is not hydrogen. The reaction of ethyl (dimethylsulfuranylidene)acetate (EDSA) with [60]fullerene gives [6,6]-methanofullerene (eq 5).



(4)

A **B**

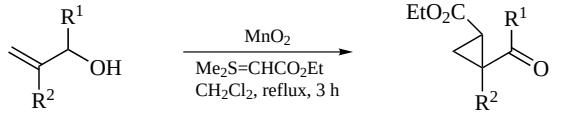
R^1	R^2	R^3	Yield (%)	Yield (%)
i-Pr	H	H	70	–
Me	Me	H	65	–
R^1, R^2 = $–(CH_2)_5–$	–	H	68	–
i-Pr	H	Me	20	76
i-Pr	H	Et	12	77
R^1, R^3 = $–(CH_2)_4–$	H	–	Trace	91



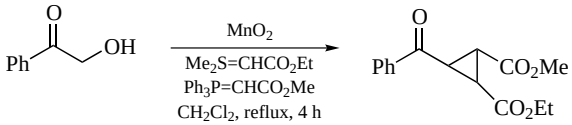
(5)

The diastereoselectivity of the reaction of cyclopentanone with EDSA has been improved from 69:31 to 98:2 by performing the reaction at room temperature in toluene rather than at 80 °C in benzene.[18]

A direct method for preparing cyclopropanes from allylic alcohols in a one-pot reaction with manganese dioxide and EDSA has been developed (eq 6).[19] α-Hydroxyketones can undergo a one-pot reaction with manganese dioxide, EDSA, and a stabilized Wittig reagent (Ph_3P=CHW) to give cyclopropanes via a domino-like process involving allylic oxidation, Wittig olefination, followed by a cyclopropanation reaction sequence (eq 7).[19]

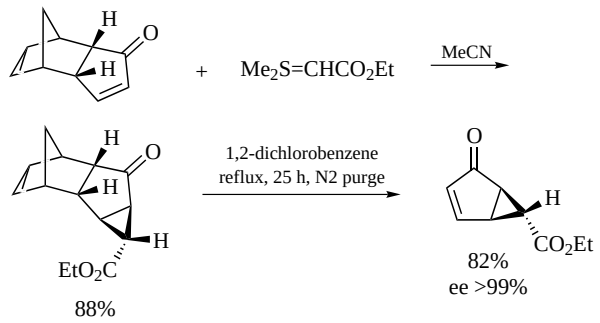


R^1 = H, Et, Ph, vinyl
R^2 = H, Me, TBSOCH$_2$
yields 53–100%
trans:*cis* >2:1 (6)



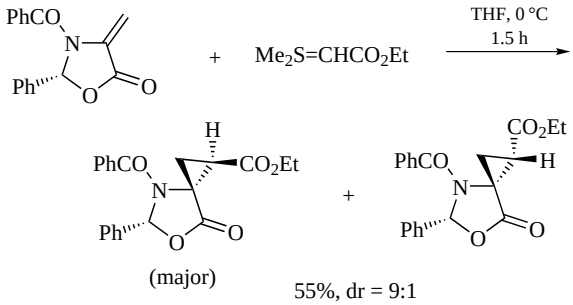
83%
(dr = 3.1:1) (7)

When the Michael receptors are chiral, diastereoselective cyclopropanation reactions are possible. Treatment of an enantiomerically pure (+)-dicyclopentadienone with EDSA gave the *exo*-cyclopropane product in 88% yield in >99% ee. Thermolysis of this adduct gave, via a retro-Diels–Alder reaction, an optically active (>99% ee) cyclopentenone in 82% yield (eq 8).[20]



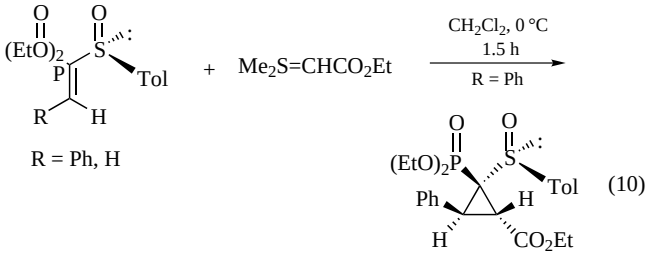
88%
82%
ee >99% (8)

Protected 2-substituted cyclopropane amino acids could be prepared from the adducts formed from the reaction of a chiral 4-methyleneoxazolidinone and EDSA (eq 9).[21]



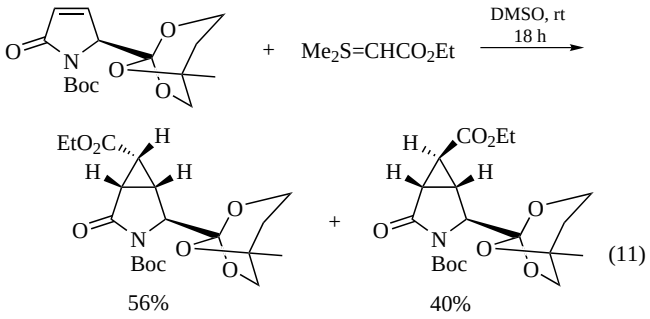
(major)
55%, dr = 9:1 (9)

Enantiomerically pure cyclopropylphosphonate derivatives were obtained from the reactions of EDSA with chiral (*S*)-(1-dimethoxyphosphoryl)-vinyl *p*-tolyl sulfoxides. The reaction of EDSA with the 2-phenyl-substituted vinyl *p*-tolyl sulfoxide substrate was high yielding and proceeded with good diastereoselectivity (eq 10),[22] while the unsubstituted analog (R = H) gave four diastereomeric adducts.[23]



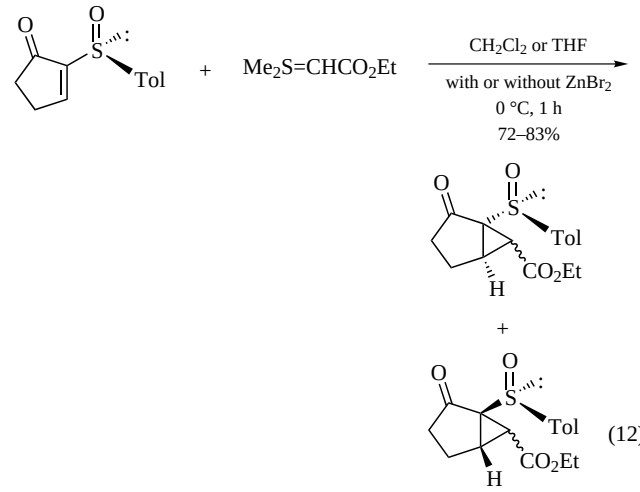
R = Ph, H
91%, dr = 8:1 (10)

Treatment of 3,4-didehydro-L-pyroglutamate, protected as a cyclic orthoester, with ESTA gave a mixture of two diastereomeric products that differed in configuration at the α-ethyl ester position (eq 11). These diastereomers could be separated and converted to enantiomerically pure, cyclopropane L-glutamate analogs.[24]



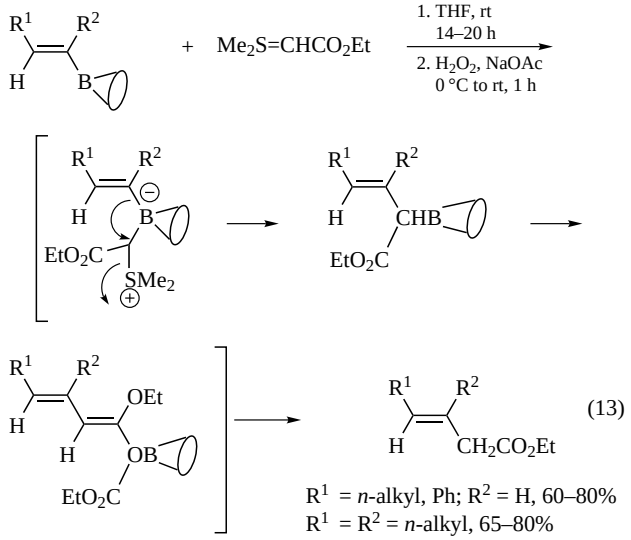
56%
40% (11)

The reaction of EDSA with 2-[(*S*)-tolylsulfinyl]cyclopent-2-en-1-one gave mixtures of four diastereomeric adducts that could be separated (eq 12). The π-facial selectivity and *endo* vs. *exo* selectivity could be varied as a function of the method of generating EDSA, the nature of the solvent, and the counterion of the precursor to EDSA.[25]



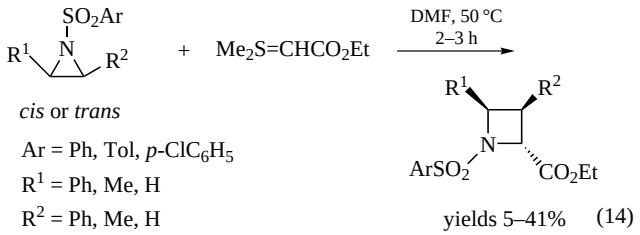
(12)

Synthesis of β,γ-Unsaturated Esters. Treatment of 9-alkenyl-9-BBN derivatives with ESDA followed by an oxidative workup provided stereodefined β,γ-unsaturated esters in good overall yields (eq 13).[26] This method has been extended to the synthesis of related β,γ-unsaturated esters in which R^1 and R^2 are different alkyl substituents.[27]



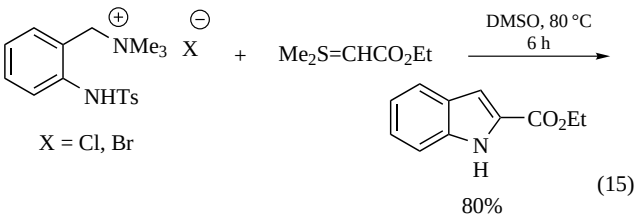
(13)

Synthesis of Azetidines. The reactions of *cis*- or *trans*-*N*-arylsulfonylaziridines with ESDA provide a synthesis of 1-arylsulfonyl-2-ethyoxycarbonyl azetidines in a diastereoseolective manner (eq 14).[28] The *trans*-*N*-arylsulfonylaziridines are much more reactive and give better yields of the azetidine products. The *trans*- and *cis*-*N*-arylsulfonylaziridines were found to be in equilibrium in these reaction mixtures with only the *trans*-isomer reacting to give the azetidine product. The relative configuration of the carbons bearing the substituents R^1 and R^2 is consistent with an S_N2 mechanism in the key aziridine ring-opening step.

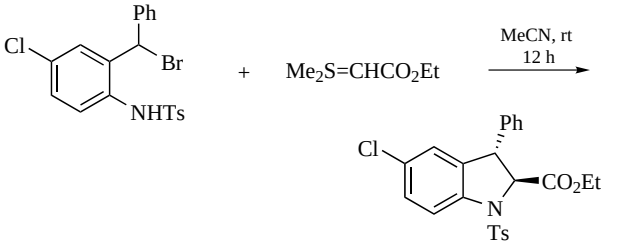


(14)

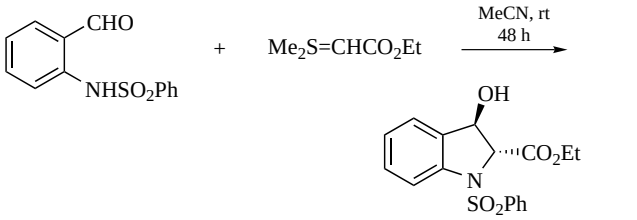
Synthesis of Indoles. Treatment of 2-(tosylamino)benzyltrimethylammonium halides with ESDA (2.6 equiv) in DMSO at 80 °C gave ethyl indole-2-carboxylate in 80% yield (eq 15). The use of 1.1 equiv of ESDA gave a mixture of the indole and the indoline precursor.[29] A similar reaction on a related 2-(tosylamino)-α-phenylbenzyl bromide using 2.0 equiv of ESDA at room temperature gave a 2,3-*trans*-indoline derivative (eq 16),[30] while 2-(benzenesulfonylamino)benzaldehyde, upon treatment with 2 equiv of ESDA, gave a 2,3-*trans*-indoline derivative (eq 17).[31] An oxirane intermediate was proposed with the second equivalent of ESDA acting as a base to deprotonate the sulfonamide prior to indoline ring formation.



(15)

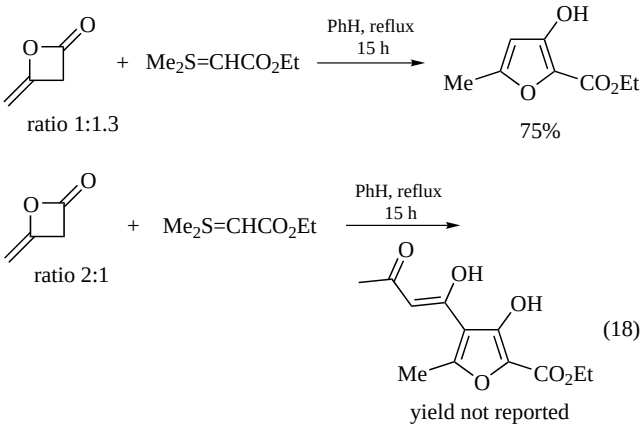


(16)



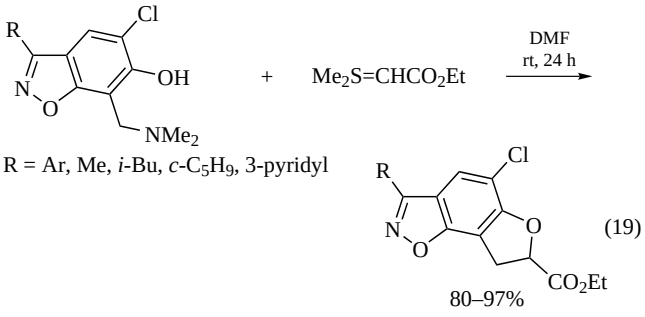
(17)

Synthesis of Furans. The reaction between ESDA (1.3 equiv) and diketene in benzene with heating at reflux for 15 h gave ethyl 3-hydroxy-5-methylfuran-1-carboxylate (eq 18). However, when 0.5 equiv of ESDA was used, the analogous 4-substituted product was obtained via further reaction with ketene (eq 18).[32]



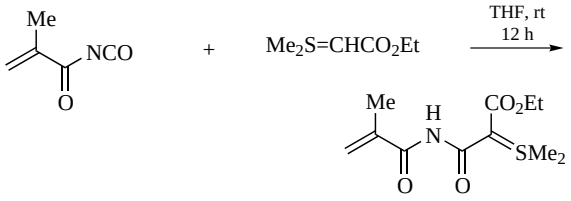
(18)

Synthesis of Dihydrobenzofurans. Treatment of *ortho*-*N*,*N*,-dimethylaminomethylphenols with ESDA gave 1,2-dihydro-benzofurans in high yields (eq 19).[33]



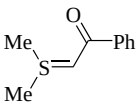
(19)

Stabilized Sulfur Ylides. Treatment of methacryloyl isocyanate with ESDA gave the corresponding carbamoyl ylide (eq 20).[34]

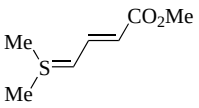


(20)

Related Reagents. Two similar carbonyl-stabilized dimethylsulfonium methylides (**1** and **2**) have been reported to function as cyclopropanating reagents in a fashion analogous to EDSA.[14]



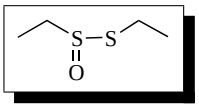
(1)



(2)

1. (a) Speziale, A. J.; Tung, C. C.; Ratts, K. W.; Yao, A., *J. Am. Chem. Soc.* **1965**, *87*, 3460. (b) Payne, G. B., *J. Org. Chem.* **1967**, *32*, 3351. (c) Payne, G. B., *J. Org. Chem.* **1968**, *33*, 1284. (d) Payne, G. B., *J. Org. Chem.* **1968**, *33*, 1285. (e) Payne, G. B., *J. Org. Chem.* **1968**, *33*, 3517.
2. Arbale, A. A.; Naik, R. H.; Kulkarni, G. H., *Indian J. Chem., Sect. B* **1990**, *29B*, 568.
3. Mack, H.; Hanack, M., *Liebigs Ann. Chem.* **1989**, 833.
4. Wender, P. A.; Hillemann, C. L.; Szymonifka, M. J., *Tetrahedron Lett.* **1980**, *21*, 2205.
5. Wanner, M. J.; Hageman, J. J. M.; Koomen, G. J.; Pandit, U. K., *Recl. Trav. Chim. Pays-Bas* **1978**, 97, 211.
6. Mitra, R. B.; Muljiani, Z.; Reddy, G. B., *Synth. Commun.* **1986**, *16*, 1099.
7. Rao, A. V. R.; Rao, M. N.; Garyali, K., *Synth. Commun.* **1984**, *14*, 557.
8. Iwata, C.; Suzuki, K.; Aoki, S.-I.; Okamura, K.; Yamashita, M.; Takahashi, I.; Tanaka, T., *Chem. Pharm. Bull.* **1986**, *34*, 4939.
9. House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972.
10. Newman, M. S.; Magerlein, B. J., *Org. React.* **1949**, *5*, 413.
11. Adams, J.; Hoffman, L., Jr.; Trost, B. M., *J. Org. Chem.* **1970**, *35*, 1600.
12. Dave, V.; Warnhoff, E. W., *Org. React.* **1970**, *18*, 217.
13. (a) Uchytil, B.; Procházka *Collect. Czech. Chem. Commun.* **1974**, *39*, 2085. (b) Ashton, W. T.; Meurer, L. C.; Cantone, C. L.; Field, A. K.; Hannah, J.; Karkas, J. D.; Liou, R.; Patel, G. F.; Perry, H. C.; Wagner, A. F.; Walton, E.; Tolman, R. L., *J. Med. Chem.* **1988**, *31*, 2304.
14. (a) Neff, J. R.; Gruetzmacher, R. R.; Nordlander, J. E., *J. Org. Chem.* **1974**, *39*, 3814. (b) Chiericato, M.; Croce, P. D.; Licandro, E., *J. Chem. Soc., Perkin Trans. 1* **1979**, 211.
15. Kumaran, G.; Kulkarni, G. H., *Synthesis* **1995**, 1545.
16. Wang, Y.; Cao, J.; Schuster, D. I.; Wilson, S. R., *Tetrahedron Lett.* **1995**, *36*, 6843.
17. Wang, Y.; Schuster, D. I.; Wilson, S. R.; Welch, C. J., *J. Org. Chem.* **1996**, *61*, 5198.
18. S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D., *J. Med. Chem.* **1997**, *40*, 528.
19. McAllister, G. D.; Oswald, M. F.; Paxton, R. J.; Raw, S. A.; Taylor, R. J. K., *Tetrahedron* **2006**, *62*, 6681.
20. Moher, E. D., *Tetrahedron Lett.* **1996**, *37*, 8637.
21. Pyne, S. G.; Schafer, K.; Skelton, B. W.; White, A. H., *Aust. J. Chem.* **1998**, *51*, 127.
22. Midura, W. H.; Mikolajczyk, M., *Tetrahedron Lett.* **2002**, *43*, 3061.
23. Midura, W. H.; Krysiak, J. A.; Mikolajczyk, M., *Tetrahedron: Asymmetry* **2003**, *14*, 1245.
24. Oba, M.; Nishiyama, N.; Nishiyama, K., *Tetrahedron* **2005**, *61*, 8456.
25. Mikolajczyk, M.; Midura, W. H.; Michedkina, E.; Filipczak, A. D.; Wieczorek, M. W., *Helv. Chim. Acta* **2005**, *88*, 1769.
26. Deng, M.; Li, N.; Huang, Y., *J. Org. Chem.* **1992**, *57*, 4017.
27. Deng, M.; Li, N.; Huang, Y., *J. Org. Chem.* **1993**, *58*, 1949.
28. Nadir, U. K.; Arora, A., *J. Chem. Soc., Perkin Trans. 1* **1995**, *20*, 2605.
29. Dalla Croce, P.; Ferraccioli, R.; La Rosa, C., *Heterocycles* **1996**, *43*, 2397.
30. Cremonesi, G.; Dalla Croce, P.; La Rosa, C., *Heterocycles* **2005**, *66*, 557.
31. Cremonesi, G.; Dalla Croce, P.; Fontana, F.; La Rosa, C., *Heterocycles* **2007**, *73*, 873.
32. Lutz, T. G.; Clevette, D. J.; Hoveyda, H. R.; Karunaratne, V.; Nordin, A.; Sjoeberg, S.; Winter, M.; Orvig, C., *Can. J. Chem.* **1994**, *72*, 1362.
33. Sato, H.; Dan, T.; Onuma, E.; Tanaka, H.; Aoki, B.; Koga, H., *Chem. Pharm. Bull.* **1991**, *39*, 1760.
34. Hatta, T.; Ishibashi, S.; Tsuge, O., *Org. Prep. Proced. Int.* **2001**, *33*, 173.

S-Ethyl Ethanethiosulfinate



[18542-39-7] $C_4H_{10}OS_2$ (MW 138.25)
InChI = 1/C4H10OS2/c1-3-6-7(5)4-2/h3-4H2,1-2H3
InChIKey = FIWQKOIUXFENIV-UHFFFAOYAY

(thiol protecting agent, thioacetaldehyde, and ethanesulfenic acid precursor)

Physical Data: bp 63–65.5 °C/2 mmHg;[1] 1.104 g cm^{-3}.[2]

Solubility: soluble in most organic solvents[2] and partially soluble (approx. 11%) in water.[3]

Form Supplied in: not commercially available.

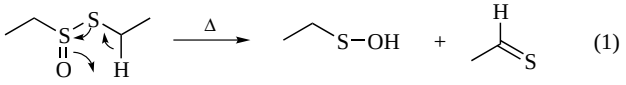
Analysis of Reagent Purity: ^{1}H NMR,[4] ^{13}C NMR,[5,6] elemental analysis.[2]

Preparative Method: the reagent is prepared by oxidation of ethyl disulfide with *m*-CPBA at 0 °C in 56% yield.[1,2,7,8] Alternatively, it can be prepared by photooxidation of ethyl disulfide with singlet oxygen.[9,10]

Purification: vacuum distillation.

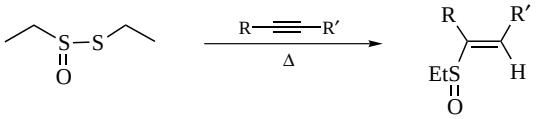
Handling, Storage, and Precautions: thermally unstable and should be stored in dark at temperatures of −20 °C or lower if it is not to be used immediately; upon standing at room temperature it spontaneously disproportionates to form a mixture of disulfide and sulfonate as major product;[11] contact with skin may cause severe dermatitis;[11] also unstable towards bases yielding disulfide and sulfur dioxide.[2]

Pyrolysis. The facile pyrolysis of *S*-ethyl ethanethiosulfinate affords ethanesulfenic acid and thioacetaldehyde (eq 1).



(1)

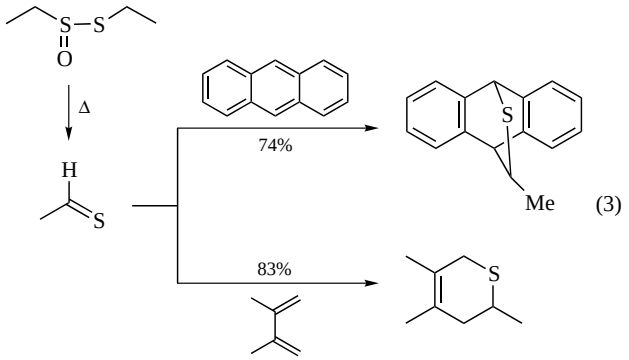
Subsequent trapping of the ethanesulfenic acid with acetylenes stereospecifically provides α,β-unsaturated sulfoxides (eq 2).[12,13]



(2)

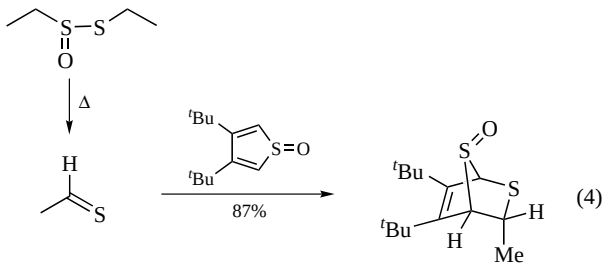
R	R′	Yield (%)
H	CO_2Me	76
Ph	H	91
n-C_5H_{11}	H	33

Similarly, the thioacetaldehyde can be trapped with both aliphatic and aromatic 1,3-dienes such as anthracene and 2,3-dimethylbutadiene in good yields (eq 3). However, yields are reduced in dimethylformamide as solvent.[14–16]



(3)

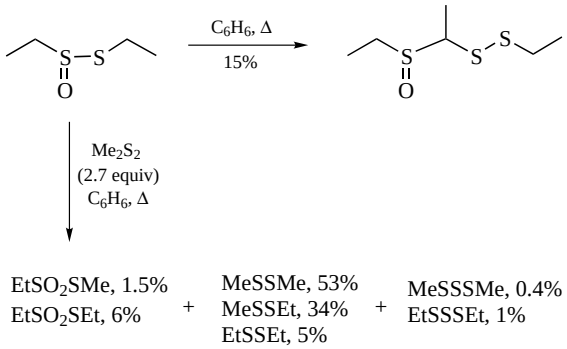
The hetero Diels–Alder reaction of 3,4-di-*tert*-butylthiophene 1-oxide with the thioacetaldehyde generated by thermolysis of *S*-ethyl ethanethiosulfinate proceeded exclusively syn to the S=O bond and in the endo mode (eq 4).[17]



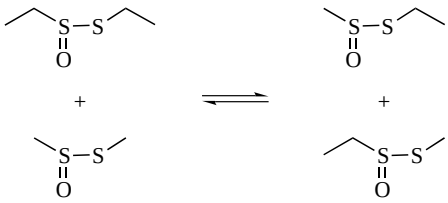
(4)

In the absence of a trapping agent, pyrolysis of the *S*-ethyl ethanethiosulfinate produces the α-sulfinyl disulfide, 4-methyl-3,5,6-trithiaoctane 3-oxide in moderate yield (eq 5).[18] In presence of the methyl disulfide, the pyrolysis produces a complex mixture of products (eq 5).[12]

Mixing of *S*-ethyl ethanethiosulfinate with *S*-methyl methanethiosulfinate in the dark, either neat or in benzene solution, rapidly establishes an equilibrium with the complete scrambling of the sulfenyl and sulfinyl fragments (eq 6).[12]

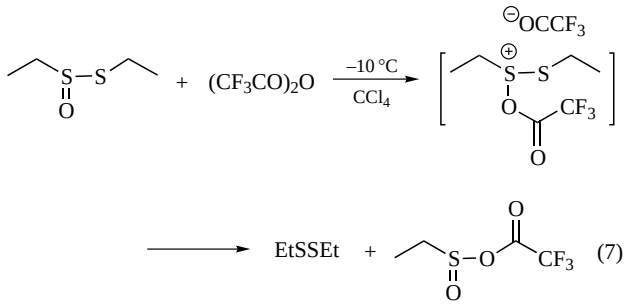


(5)



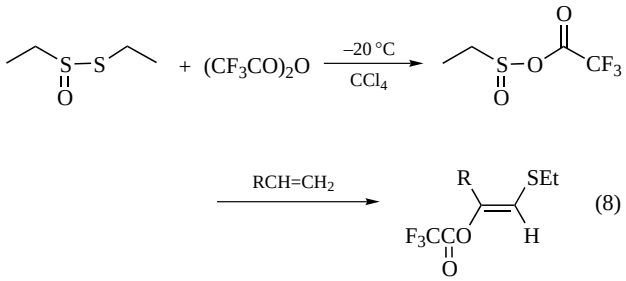
(6)

Pummerer Rearrangement. *S*-Ethyl ethanethiosulfinate on treatment with trifluoroacetic anhydride produces an approximately equimolar mixture of the corresponding disulfide and sulfinyl trifluoroacetates. The reaction proceeds with the initial acylation of the sulfinyl oxygen followed by formation of the sulfenyl trifluoroacetate as transient intermediate (eq 7).[19,20] This sulfinyl carboxylate is only stable in solution at room temperature, as attempted isolation was unsuccessful and led to the isolation of the sulfonate and the disulfide.[19]



(7)

However, in presence of an olefin the same reaction produces the corresponding β-trifluoroacetoxy sulfides by electrophilic 1,2-addition of sulfenyl trifluoroacetate to the olefin (eq 8). The addition takes place stereospecifically in trans fashion. In the case of monoalkyl substituted ethylenes, the kinetically controlled



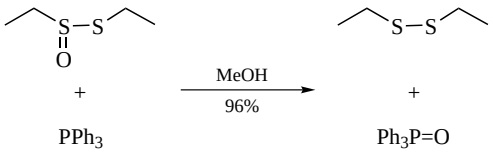
(8)

R: C_6H_{13}, 91%

R: ^{i}Pr, 81%

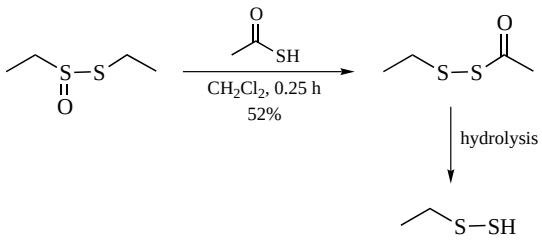
product is the anti-Markownikoff β-trifluoroacetoxy sulfide, which can be transformed to the regioisomeric Markownikoff product upon heating.[20] Interestingly, reaction with acetic anhydride does not produce the Pummerer product.[1]

Reaction with PPh_3. Triphenylphosphine reacts with the *S*-ethyl ethanethiosulfinate to produce ethyl disulfide at room temperature in excellent yield (eq 9).[8]



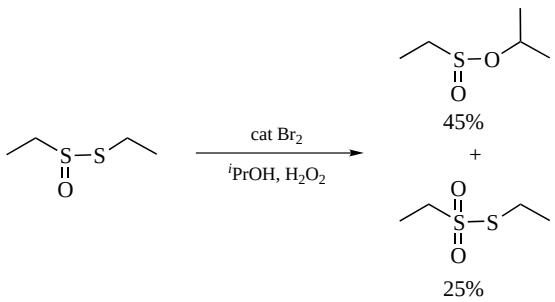
(9)

Synthesis of Acetyl Ethyl Disulfides. *S*-Ethyl ethanethiosulfinate can be rapidly converted to acetyl ethyl disulfide in moderate yield by reaction with thioacetic acid (eq 10). Advantageously, the liberated ethylsulfenic acid can regenerate the thiosulfinate via dehydration. Acetyl ethyl disulfide is a key intermediate for the synthesis of the ethyl hydrodisulfides, which can be prepared by acid catalyzed hydrolysis.[21]



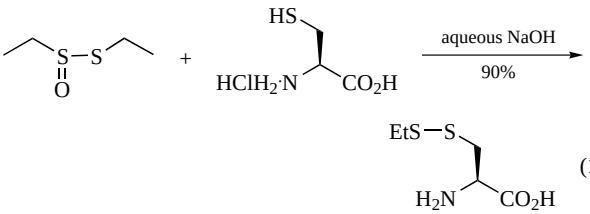
(10)

Synthesis of Sulfinate Ester. *S*-Ethyl ethanethiosulfinate can be transformed to the stable sulfinate esters by replacement of the sulfenyl group with catalytic bromine and H_2O_2 in the presence of an alcohol such as isopropanol (eq 11).[22] However, in absence of the alcohol, the thiosulfinate disproportionates rapidly under these conditions and forms a mixture of thiosulfonate and disulfide.

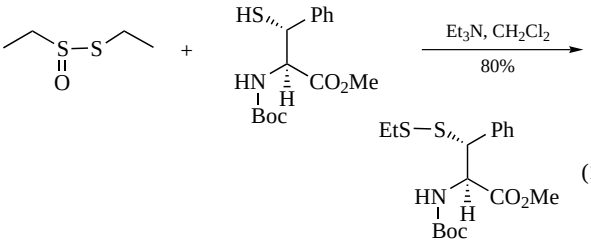


(11)

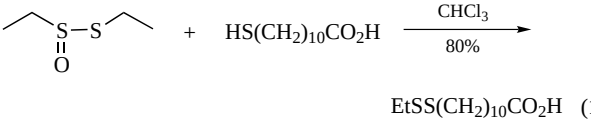
Protection of Thiols as Disulfides. The protection of free thiols as unsymmetrical ethyl disulfides can be efficiently performed with *S*-ethyl ethanethiosulfinate in high yield. The advantages of this protocol are (i) it operates with a very inexpensive starting material; (ii) it can be performed on a wide variety of substrates such as protected[23] and unprotected[3] thiol containing amino acids (eqs 12 and 13), lipids (eq 14),[24] and aliphatic amines (eq 15);[25] (iii) the liberation of the thiol by reduction of the ethyl disulfide can be performed either with tributylphosphine[24,26] or with a thiol such as 2-mercaptoethane sulfonate sodium salt.[23] Under similar reaction conditions, the *S*-ethyl ethanethiosulfonate also performed the same transformation.[3]



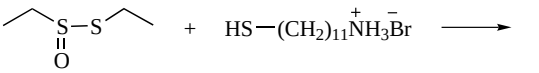
(12)



(13)



$EtSS(CH_2)_{10}CO_2H$ (14)



$EtSS-(CH_2)_{11}\overset{+}{N}H_3\overset{-}{B}r$ (15)

Unsymmetrical thiosulfinates can be oxidized selectively with sodium metaperiodate in aqueous media to the corresponding thiosulfonates quantitatively.[27]

1. Furukawa, N.; Morishita, T.; Akasaka, T.; Oae, S., *J. Chem. Soc., Perkin Trans. 2* **1980**, 432.
2. Small, L. D.; Bailey, J. H.; Cavallito, C. J., *J. Am. Chem. Soc.* **1947**, *69*, 1710.
3. Small, L. D.; Bailey, J. H.; Cavallito, C. J., *J. Am. Chem. Soc.* **1949**, *71*, 3565.
4. Legler, L. E.; Jindal, S. L.; Murray, R. W., *Tetrahedron Lett.* **1972**, *13*, 3907.
5. Bass, S. W.; Evans, S. A., *J. Org. Chem.* **1980**, *45*, 710.
6. Freeman, F.; Angeletakis, C. N., *J. Org. Chem.* **1982**, *47*, 4194.
7. Hogg, D. R. In *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D. Eds.; Pergamon Press: Oxford, 1979; Vol. 3, p 261.
8. Carson, J. F.; Wong, F. F., *J. Org. Chem.* **1961**, *26*, 1467.
9. Clennan, E. L.; Wang, D.; Zhang, H.; Clifton, C. H., *Tetrahedron Lett.* **1994**, *35*, 4723.
10. Murray, R. W.; Smetana, R. D.; Block, E., *Tetrahedron Lett.* **1971**, *12*, 299.

11. Block, E.; O'Connor, J., *J. Am. Chem. Soc.* **1974**, *96*, 3921.
12. Block, E.; O'Connor, J., *J. Am. Chem. Soc.* **1974**, *96*, 3929.
13. Block, E., *J. Am. Chem. Soc*. **1972**, *94*, 642.
14. Baldwin, J. E.; Lopez, R. C. G., *Tetrahedron* **1983**, *39*, 1487.
15. Baldwin, J. E.; Lopez, R. C. G., *J. Chem. Soc., Chem. Commun.* **1982**, 1029.
16. Collier, S. J., *Sci. Synth.* **2004**, *27*, 177.
17. Takayama, J.; Fukuda, S.; Sugihara, Y.; Ishii, A.; Nakayama, J., *Tetrahedron Lett.* **2003**, *44*, 5159.
18. Block, E.; O'Connor, J., *J. Am. Chem. Soc.* **1973**, *95*, 5048.
19. Morishita, T.; Furukawa, N.; Oae, S., *Tetrahedron* **1981**, *37*, 3115.
20. Morishita, T.; Furukawa, N.; Oae, S., *Tetrahedron* **1981**, *37*, 2539.
21. Freeman, F.; Huang, B.-G.; Lin, R. I.-S., *Synthesis* **1994**, 699.
22. Takata, T.; Oae, S., *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3937.
23. Crich, D.; Banerjee, A., *J. Am. Chem. Soc*. **2007**, *129*, 10064.
24. Samuel, N. K. P.; Singh, M.; Yamaguchi, K.; Regan, S. L., *J. Am. Chem. Soc.* **1985**, *107*, 42.
25. Niwa, M.; Morikawa, M.; Nabeta, T.; Higashi, N., *Macromolecules* **2002**, *35*, 2769.
26. Wu, B.; Chen, J. H.; Warren, J. D.; Chen, G.; Hua, Z. H.; Danishefsky, S. J., *Angew. Chem., Int. Ed.* **2006**, *45*, 4116.
27. Kirn, Y. H.; Takata, T.; Oae, S., *Tetrahedron Lett.* **1978**, *19*, 2305.

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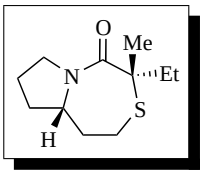
4-Ethylhexahydro-4-methyl-(4*S*,9a*S*)-pyrrolo[1,2-*d*][1,4]thiazepin-5(4*H*)-one



[481047-13-6] $C_{11}H_{19}NOS$ (MW 213.34)

InChI = 1/C11H19NOS/c1-3-11(2)10(13)12-7-4-5-9(12)6-8-14-11/h9H,3-8H2,1-2H3/t9-,11-/m0/s1

InChIKey = GGNLYDGKZKRGPC-ONGXEEELBB

(highly stereoselective chiral auxiliary for quaternary carbon center generation)

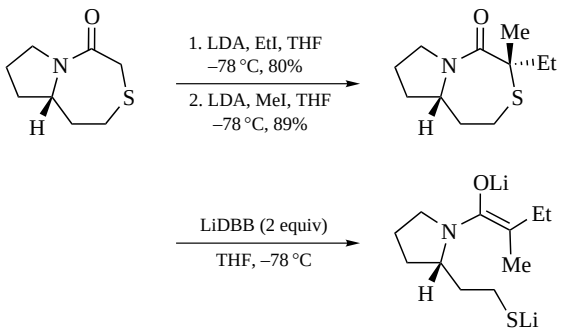
Solubility: soluble in THF.

Form Supplied in: not commercially available.

Preparative Methods: successive alkylation of (7*S*)-1-aza-4-thiabicyclo[5.3.0]-2-decanone with ethyl iodide and methyl iodide (eq 1).

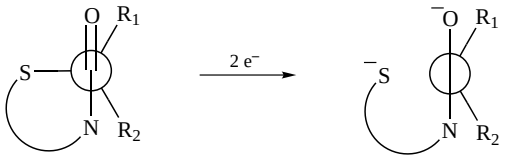
Purification: flash column chromatography on silica gel, eluted with 20% ethyl acetate in hexanes.

This reagent serves as a precursor to stereochemically defined, fully substituted amide enolates and so provides a method for stereoselective quaternary carbon formation. The two-electron reduction of α,α-dialkylated bicyclic thioglycolate lactams, prepared by sequential alkyaltion of lactam in THF with LDA in the presence of LiCl, provides disubstituted amide enolates (eq 1).[1]



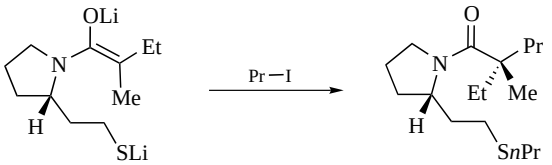
(1)

Because two alkyl groups (R^1 and R^2) are installed stereoselectively at the α-position, and the O–C–C–S dihedral angle is held close to 90 ° by the bicyclic system, bond rotation does not occur about the carbonyl-carbon/α-carbon bond during the two-electron reduction process (eq 2).[2]



(2)

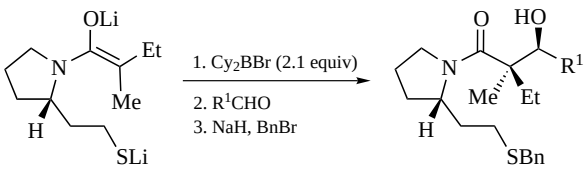
The alkylation with unactivated primary alkyl iodides has been accomplished with high selectivities using the α,α-disubstituted *Z*-amide without the need for cyclic enolates or metal chelates (eq 3).[2]



(3)

83%, >95% de

The α,α-disubstituted thioglycolate amide was successfully incorporated in highly diastereoselective aldol reaction with aromatic and α,β-unsaturated aldehydes through transmetallation of the enolates with dicyclohexylboron bromide (eq 4).[3]

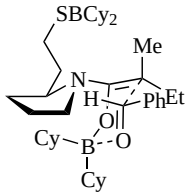


(4)

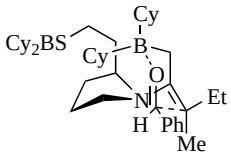
R^1	*syn*:*anti*	de (*syn*)	Yield (%)
Ph-	91:1	94	80
4-(MeO)Ph-	91:1	98	83
4-BrPh-	93:7	99	81
(*E*)-PhCH=CH-	91:9	99	63
CH_2=C(Me)-	98:2	95	44
(*E*)-MeCH=C(Me)-	91:9	91	95

It is suggested that the enolate is held in a pseudoequatorial position to minimize steric interactions of the enolate with the pyrrolidine ring in the transition state. In this manner, a significant *syn*-pentane interaction between the enolate oxygen and the pseudoaxial thioethylene chain in the alternative transition state is avoided.

Potential transition states of aldol reactions



Favored



Disfavored

1. Manthorpe, J.; Gleason, J., *J. Am. Chem. Soc.* **2001**, *123*, 2091.
2. Manthorpe, J.; Gleason, J., *Angew. Chem., Int. Ed.* **2002**, *41*, 2338.
3. Burke, E.; Gleason, J., *Org. Lett.* **2004**, *6*, 405.

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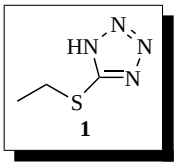
5-Ethylthio-1*H*-tetrazole



1

[89797-68-2] $C_3H_6N_4S$ (MW 130.17)

InChI = 1/C3H6N4S/c1-2-8-3-4-6-7-5-3/h2H2,1H3,(H,4,5,6,7)/f/h4H

InChIKey = GONFBOIJNUKKST-JLSKMEETCS

(reagent used a powerful activator in DNA and RNA syntheses)

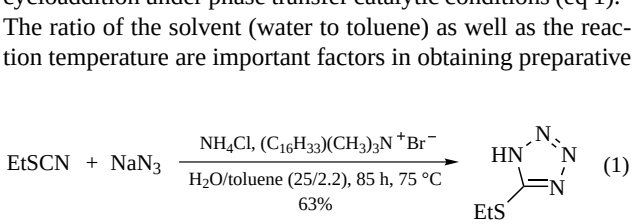
Physical Data: mp 86–88 °C.[1,2]

Solubility: soluble in CH_3CN, DMF.

Purity: recrystallized from toluene.

Analysis of Reagent Purity: IR, UV, elemental analysis.[2]

Preparative Methods: the title reagent **1** is prepared from the corresponding alkyl thiocyanate and sodium azide through a [2+3] cycloaddition under phase transfer catalytic conditions (eq 1).[1] The ratio of the solvent (water to toluene) as well as the reaction temperature are important factors in obtaining preparative yields of the alkylthiotetrazoles. 5-Ethylthio-1*H*-tetrazole has also been prepared using DMF as solvent albeit in much lower yield.[2]



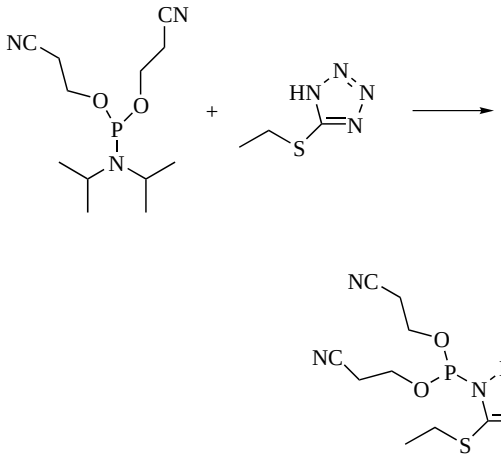
(1)

1

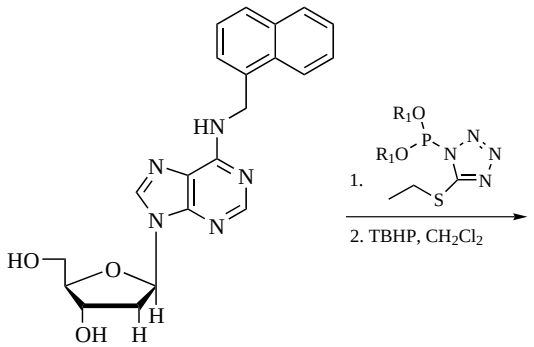
Handling, Storage, and Precautions: stable reagent; stored under argon, may be toxic.

Introduction. Tetrazoles have widespread applications in medicinal chemistry as well as in energetic materials.[3] 5-Alkylthiotetrazoles, especially 5-ethylthio-1*H*-tetrazole (**1**), serve as powerful activators in DNA and RNA syntheses.[4,5] The title compound is a better activator than the corresponding 5-alkyl or 5-aryltetrazoles due to the presence of the alkylthio group which renders the tetrazole more acidic.[2] **1** is considerably more soluble in acetonitrile than simple alkyltetrazoles, and the higher concentration results in a better activator performance.[4,5]

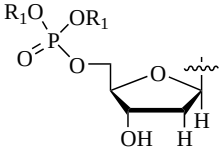
Selective Phosphitylation of the Primary Hydroxyl Group of Nucleosides. 5-Ethylthio-1*H*-tetrazole has been used for the selective 5′-phosphitylation of nucleosides.[6] The commonly accepted mechanism involves protonation of a phosphoramidite by the weakly acidic tetrazole, followed by nucleophilic attack by tetrazolide ion giving a tetrazoyl phosphoramidite (**2**) (eq 2). The nucleophilic attack of the 5′-hydroxyl group then produces the phosphite triester, which is then carried through further transformations (eq 3).[6,7]



(2)

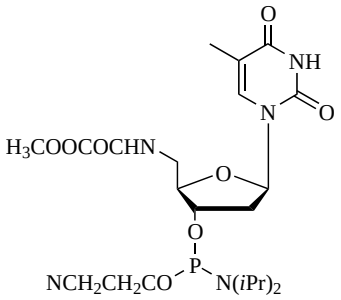


$R_1 = (CH_2)_2CN$



(3)

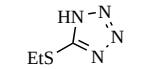
Catalyst in Oligonucleotide Derivatization. New terminus modifiers, bearing a phosphoramidite moiety and a methoxyoxalamido (MOX) precursor group, have been coupled onto the 5′-end of a synthetic oligodeoxyribonucleotide in the last step of an automated synthesis to form the MOX precursor oligonucleotide (eq 4).[8] It is observed that the coupling time is greatly reduced in the presence of a powerful catalyst such as 5-ethylthio-1*H*-tetrazole. The MOX groups can then be post-synthetically derivatized with an appropriate primary amine to construct a 5′-modified oligonucleotide.[8,9]



MOX modifier

\+ $(Tp)_9T$

10mer Oligothymidine



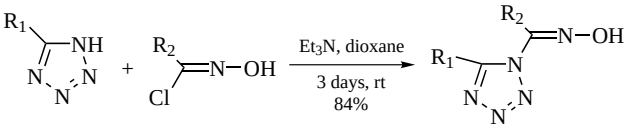
MOX modified oligothymidine (4)

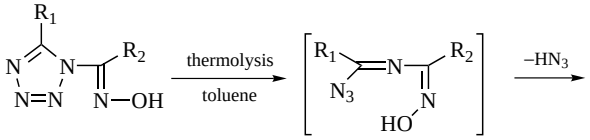
Activator in the Synthesis of RNA. 5-Ethylthio-1*H*-tetrazole has been used as an activator in the automated synthesis of a 14mer RNA sequence (5′>GAGCCUGGGAGCUC<3′). The key step in this automated synthesis by the phosphoramidite approach is the tetrazole-mediated coupling of a 5′-*O*-DMT-nucleoside-3′-*O*-phosphoramidite with the 5′-hydroxyl group of the growing chain anchored to a polymeric support. It was found that 5-ethylthio-1*H*-tetrazole as an activator gave a superior product with sixfold excess of phosphoramidite and 15 min coupling time.[10] These concentrations and coupling times are much less than those required with 1*H*-tetrazole as an activator.[11]

1,3-Addition Reactions of Azoles. 1,3-Addition reactions of azoles with nitrile oxides and nitrile imines have been carried out by dissolving equimolar amounts of the azole and the 1,3-dipole precursor (hydroximoyl chloride or hydrazonoyl halide) in an appropriate solvent at room temperature in the presence of excess triethylamine (eq 5).[12] The additions yielded mixtures of 1- and 2-substituted tetrazoles with the ratio depending mainly on the substituent in the 5-position of the tetrazole ring (eqs 5 and 6).[12]

On thermolysis in a suitable sovent, these 1,2- adducts (eq 5) and 1,3-adducts (eq 6) afforded almost quantitative yields of substituted heterocycles.

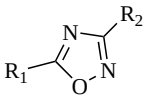
Decomposition at Higher Temperatures. It has been demonstrated that *S*-substituted mercaptotetrazoles, upon heating slightly above their melting points, yield hydrazoic acid and the corresponding organic thiocyanates (eq 7).[2]



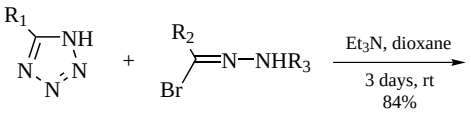


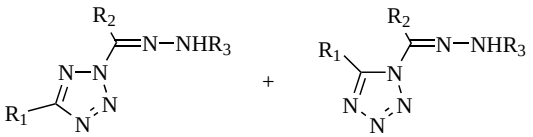
R_1 = SEt

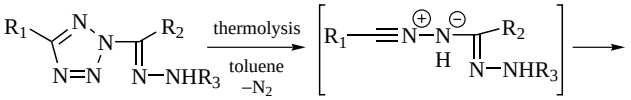
R_2 = 2,4,6-$(CH_3)_3$-C_6H_2

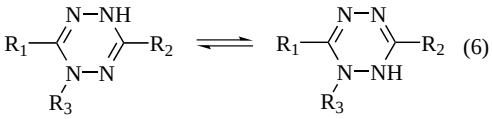


(5)







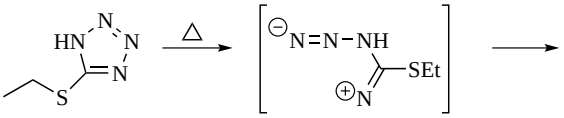


(6)

R_1= SEt

R_2 = *t*-Bu

R_3 = 4-NO_2-C_6H_4



HN_3 + EtSCN (7)

Related Reagents. 1*H*-Tetrazole;[13] 5-Methylthio- 1*H*-tetrazole;[14] 5-(*p*-Nitrophenyl)-1*H*-tetrazole;[15] 5-Butylthio-1*H*-tetrazole.[1]

1. LeBlanc, B. W.; Jursic, B. S., *Synth. Commun.* **1998**, *28*, 3591.
2. Leiber, E.; Enkoji, T., *J. Org. Chem.* **1961**, *26*, 4472.
3. Butler, R. N., In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Ed.; Pergamon Press: Oxford, 1988, Vol. 5, p 791.
4. Wincott, F.; Direnzo, A.; Shaffer, C.; Grimm, C.; Tracz, D.; Workman, C.; Sweedler, D.; Gonzalez, C.; Scaringe, S.; Usman, N., *Nucleic Acids Res.* **1995**, *23*, 2677.
5. Tsou, D.; Hampel, A.; Andrus, A.; Vinayak, R., *Nucleosides Nucleotides* **1995**, *14*, 1481.
6. Kennedy, K. J.; Bressi, J. C.; Gelb, M. H., *Bioorg. Med. Chem. Lett.* **2001**, *11*, 95.
7. Graham, S. M.; Pope, S. C., *Org. Lett.* **1999**, *1*, 733.
8. Polushin, N. N., *Nucleic Acids Research* **2000**, *28*, 3125.
9. Polushin, N. N., *Nucleosides, Nucleotides & Nucleic Acids* **2001**, *20*, 973.
10. Sproat, B.; Colonna, F.; Mullah, B.; Tsou, D.; Andrus, A.; Hampel, A.; Vinayak, R., *Nucleosides Nucleotides* **1995**, *14*, 255.
11. Vinayak, R.; Colonna, F.; Tsou, D.; Mullah, B.; Andrus, A.; Sproat, B., *Nucleic Acids Symposium Series* **1994**, *31*, 165.
12. Plenkiewicz, J.; Zdrojewski, T., *Bull. Soc. Chim. Belg.* **1987**, *96*, 675.
13. Claramunt, R. M.; Lopez, C.; Sanz, D.; Alkorta, I.; Elguero, J., *Heterocycles* **2001**, *55*, 2109.
14. Wright, P.; Lloyd, D.; Rapp, W.; Andrus, A., *Tetrahedron Lett.* **1993**, *34*, 3373.
15. Froehler, B. C.; Matteucci, M. D., *Tetrahedron Lett.* **1983**, *24*, 3171.

Santhosh Neelamkavil
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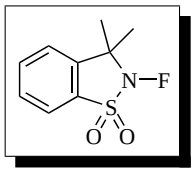
F

2-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-Dioxide



[124170-23-6] $C_9H_{10}FNO_2S$ (MW 215.24)

InChI = 1/C9H10FNO2S/c1-9(2)7-5-3-4-6-8(7)14(12,13)11(9)10/h3-6H,1-2H3

InChIKey = VMDJWSACUFRJRE-UHFFFAOYAU

(electrophilic fluorinating agent)

Alternate Name: *N*-fluoro-2,α-cumenesultam.

Physical Data: mp 115–117 °C.

Solubility: sol various organic solvents including THF, diethyl ether, CH_2Cl_2, acetonitrile.

Form Supplied in: white or slightly yellow solid, ≥98% purity; commercially available.

Analysis of Reagent Purity: ^1H and ^{19}F NMR.

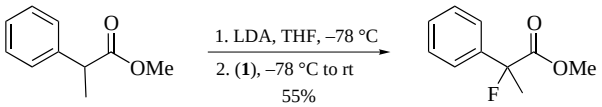
Preparative Method: pressureless fluorination on a 100 g scale with F_2 in N_2 (F_2/N_2 10% v/v) in the presence of powdered NaF in $CHCl_3/CFCl_3$ (1/1 v/v) at −40 °C.[1,2]

Purification: flash chromatography (SiO_2, CH_2Cl_2) and/or crystallization from Et_2O/pentane.

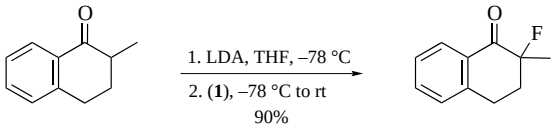
Handling, Storage, and Precautions: handle and store at rt or below; protected from light, preferably under nitrogen or argon. Thermally stable up to 200 °C; decomposes exothermally above 200 °C. Reacts with easily oxidized compounds such as iodide or tetramethylphenylenediamine. This reagent should be handled in a fume hood.

Nitrogen–fluorine bond-containing compounds are among the most useful electrophilic fluorinating agents due to their easy access, their inherent stability, and the ease with which they can be handled. 2-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (**1**) is one of the most thoroughly studied reagents, both from a preparative and a mechanistic point of view.[1–8] There is evidence, both preparative and mechanistic, that direct nucleophilic attack at fluorine occurs. Electron transfer is a competing reaction, which leads to nonfluorinated products.[5–8]

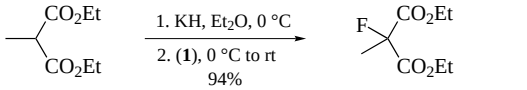
Monofluorination of Enolates. *N*-Fluorosultam (**1**) has been successfully used to prepare α-fluorocarbonyl compounds by electrophilic fluorination starting, for example, from disubstituted enolates derived from ketones, esters, and β-dicarbonyl compounds (eqs 1–3).[1] The related *N*-fluorosulfonamide reagents[9] give considerably lower yields due to the elimination of HF by proton abstraction from the carbon α to the nitrogen atom.[1]



(1)

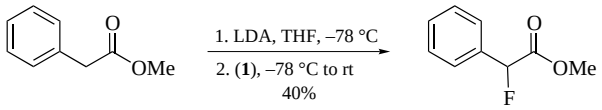


(2)

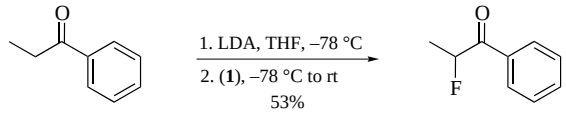


(3)

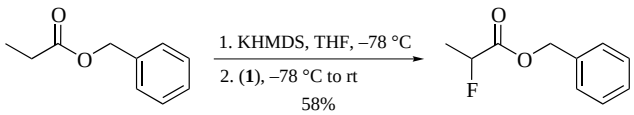
Monosubstituted enolates can be selectively monofluorinated using slightly more than 1 equiv of base and *N*-fluorosultam. The influence of the counterion is crucial and the selectivity decreases in the order Li > Na > K, although potassium hexamethyldisilazide often gives higher yields, especially with esters (eqs 4–6).[4]



(4)



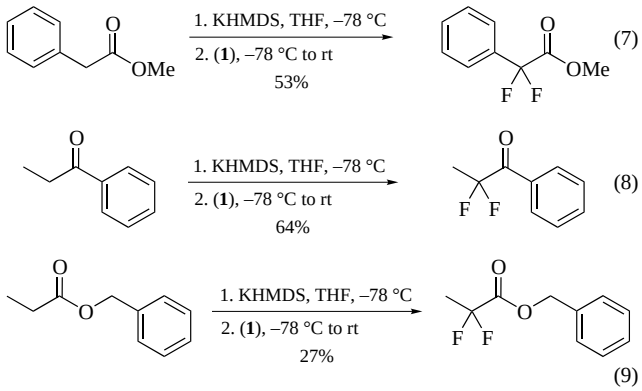
(5)



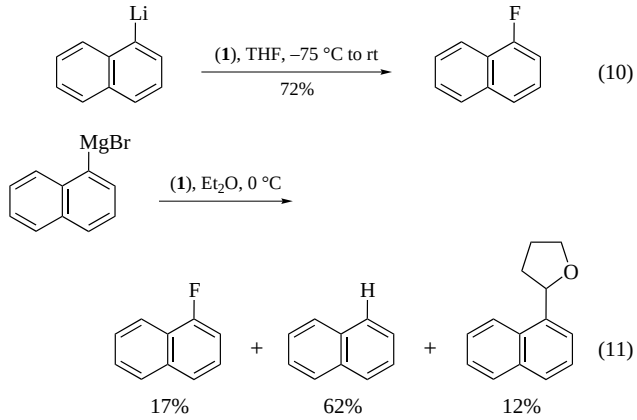
(6)

See also the related chiral *N*-fluorosultam reagents derived from camphor which allow for enantioselective fluorination with modest enantiomeric excesses (up to 75%).[10,11]

Double Fluorination of Enolates. Double fluorination of monosubstituted enolates is achieved selectively in a one-pot procedure by adding the starting carbonyl compound to 2.4–3.6 equiv of base in THF at −78 °C followed by the addition of 2.6–3.6 equiv of the *N*-fluorosultam, and warming up to room temperatures. For this process, KHMDS and potassium diisopropylamide are the bases of choice (eqs 7–9).[4]



Fluorination of Organometallic Reagents. Aryl fluorides can be prepared by reacting the corresponding aryllithium compound with (**1**) (eq 10). Grignard reagents give significantly lower yields, probably due to competing electron transfer reactions since radical-derived side products have been isolated and characterized (eq 11).[6]



For a more reactive nitrogen–fluorine bond containing reagent, see *N*-Fluoro-*N*-(phenylsulfonyl)benzenesulfonamide.[12]

1. Differding, E.; Lang, R. W., *Helv. Chim. Acta* **1989**, *72*, 1248.
2. Auer, K.; Hungerbühler, E.; Lang, R. W., *Chimia* **1990**, *44*, 120.
3. Differding, E.; Frick, W.; Lang, R. W.; Martin, P.; Schmit, C.; Veenstra, S.; Greuter, H., *Bull. Soc. Chim. Belg.* **1990**, *99*, 647.
4. Differding, E.; Rüegg, G. M.; Lang, R. W., *Tetrahedron Lett.* **1991**, *32*, 1779.
5. Differding, E.; Rüegg, G. M., *Tetrahedron Lett.* **1991**, *32*, 3815.
6. Differding, E.; Wehrli, M., *Tetrahedron Lett.* **1991**, *32*, 3819.
7. Differding, E.; Bersier, P. M., *Tetrahedron* **1992**, *48*, 1595.
8. Andrieux, C. P.; Differding, E.; Robert, M.; Savéant, J.-M., *J. Am. Chem. Soc.* **1993**, *115*, 6592.
9. Barnette, W. E., *J. Am. Chem. Soc.* **1984**, *106*, 452.
10. Differding, E.; Lang, R. W., *Tetrahedron Lett.* **1988**, *29*, 6087.
11. Davis, F. A.; Zhou, P.; Murphy, C. K., *Tetrahedron Lett.* **1993**, *34*, 3971.
12. Differding, E.; Ofner, H., *Synlett* **1991**, 187.

Edmond Differding
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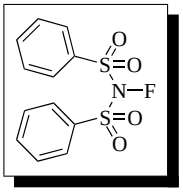
N-Fluoro-*N*-(phenylsulfonyl)benzenesulfonamide



[133745-75-2] $C_{12}H_{10}FNO_4S_2$ (MW 315.33)

InChI = 1/C12H10FNO4S2/c13-14(19(15,16)11-7-3-1-4-8-11)20(17,18)12-9-5-2-6-10-12/h1-10H

InChIKey = RLKHFSNWQCZBDC-UHFFFAOYAH

(electrophilic fluorinating agent)

Alternative Names: *N*-fluorobenzenesulfonimide; *N*-fluorobis(phenylsulfonyl)amine; *N*-fluorodibenzenesulfonimide, NFSi.

Physical Data: mp 114–116 °C.

Solubility: sol various organic solvents, including THF (0.24 g ml^{-1}), CH_2Cl_2 (0.40 g ml^{-1}), acetonitrile (0.25 g ml^{-1}), and toluene (0.09 g ml^{-1}).

Form Supplied in: white or slightly yellow solid, >98% purity; commercially available.

Analysis of Reagent Purity: ^1H and ^{19}F NMR.

Preparative Method: pressureless fluorination on a 0.2 mol scale with F_2 in N_2 (F_2/N_2 10% v/v) in the presence of powdered NaF in acetonitrile at −40 °C.[1]

Purification: flash chromatography (SiO_2, CH_2Cl_2) and/or crystallization from Et_2O.

Handling, Storage, and Precautions: handle and store at rt or below; protected from light, preferably under nitrogen or argon. Thermally stable up to 180 °C; decomposes exothermally at higher temperatures. Reacts with easily oxidized compounds such as iodide. This reagent should be handled in a fume hood.

Original Commentary

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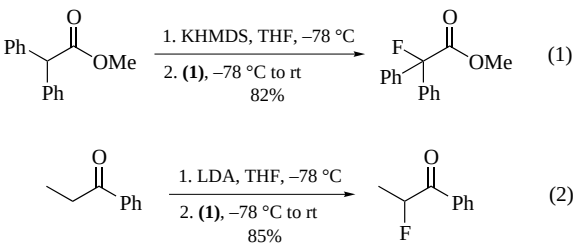
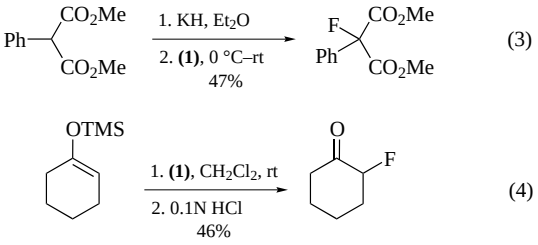
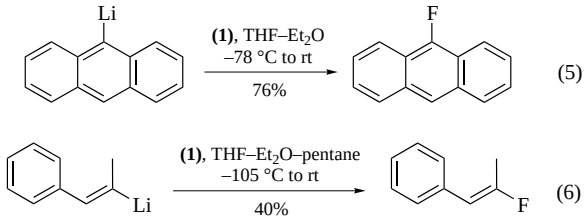
Fluorination of Enolates and Silyl Enol Ethers. *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (**1**) can be used successfully to prepare α-fluorocarbonyl compounds starting from esters, ketones, or β-dicarbonyl precursors by electrophilic fluorination of the corresponding enolates (eqs 1–3) or silyl enol ethers (eq 4).[1] Diastereoselective fluorination of enolates with **1** has recently been reported.[7]

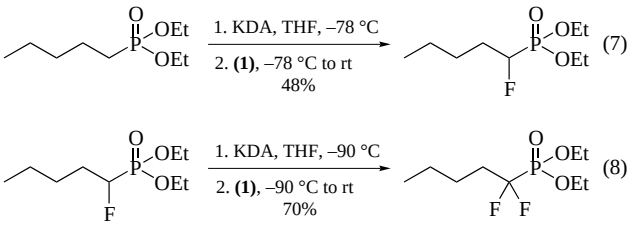




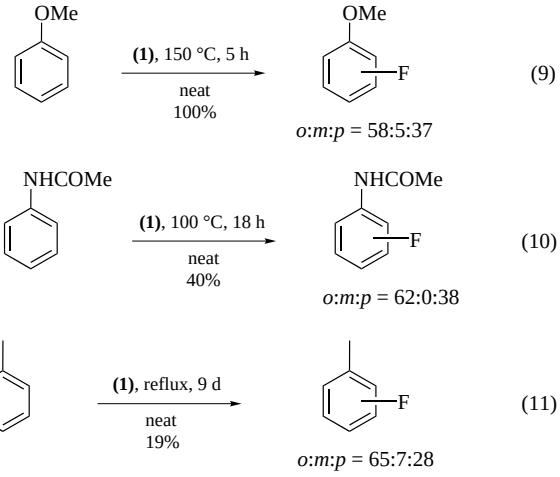
Fluorination of Organometallic Reagents. Aryl and vinyl fluorides are conveniently prepared by reacting the corresponding lithium derivatives with **1**.[1] For example, anthracenyllithium, generated from bromoanthracene with *n*-butyllithium, is fluorinated in THF at −78 °C (eq 5). 1-Phenyl-2-lithiopropene, obtained by reacting the corresponding iodoalkene with *t*-butyllithium, requires a lower reaction temperature (−105 °C, THF/Et_2O/pentane). This reaction affords the fluoroalkene with complete retention of configuration at the double bond (eq 6).



Fluorination of Alkyl Phosphonate Carbanions. α-Fluoro- and α,α-difluoroalkyl phosphonates are prepared in good yields by electrophilic fluorination of phosphonate-derived carbanions (eqs 7 and 8).[2] The yields in the reaction strongly depend on the nature of the base, potassium diisopropylamide being the base of choice. α,α-Difluoroalkyl phosphonates are obtained in 54–70% yield from the corresponding monofluorinated precursors after deprotonation at low temperature (−90 °C). In situ double fluorination starting from alkyl phosphonates by using an excess of both base and **1** give only low yields (10–20%) of α,α-difluorinated products.



Electrophilic Addition to Aromatics. Aromatic compounds are fluorinated with **1** by heating without a solvent to about 100–150 °C, or, for low-boiling compounds, up to reflux temperature.[1] Activated aromatics, such as anisole or *N*-acetylaniline, react smoothly, whereas toluene requires considerably longer reaction times and gives low yields (eqs 9–11). In all cases, the regioselectivities are consistent with an electrophilic addition mechanism: *ortho*- and *para*-substituted products predominate over the *meta*-isomers. **1** has recently been used in orthometalation-directed fluorination of aromatics.[8]



First Update

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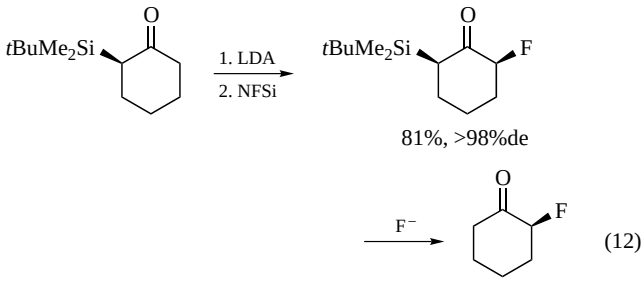
Honeywell International, Inc., Buffalo, NY, USA

N-Fluorobenzenesulfonimide (NFSi) is an electrophilic fluorinating agent that permits the incorporation of fluorine into neutral molecules as well as nucleophilic substrates ranging in strength from very reactive organometallic species to highly stabilized malonate anions. The use of NFSi does not involve any special equipment or techniques in handling, and it does not attack glass like most fluoride-containing reagents.

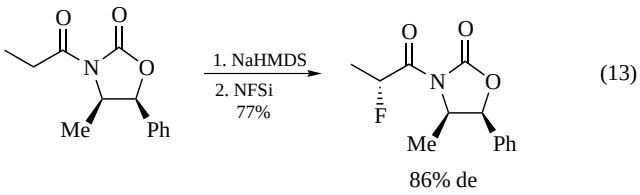
Reaction with Enolates. *N*-Fluorobenzenesulfonimide readily reacts with enolates to yield α-fluoro carbonyl compounds. Simple ketone enolates, prepared by treatment with lithium bis (trimethylsilyl)amide in THF at low temperature, are fluorinated by treatment with a molar equivalent of NFSi (eq 4).[1]

More complex carbonyl compounds and ester enolates have also been fluorinated by this method.[7,9–12] Unsaturated ketones can be fluorinated in the γ-position by generating the thermodynamic enolate with potassium hydride and HMPA, followed by complexation with 2-phenyl-1,3,2-benzodiosaborole and reaction with NFSi.[13] The regioselective and diastereoselective electrophilic fluorination of enantiopure α-silylketones with *N*-fluorobenzenesulfonimide, followed by a racemization-free cleavage of the silyl directing groups gives good yields and high enantiomeric excess of cyclic and acyclic ketones (eq 12).[14]



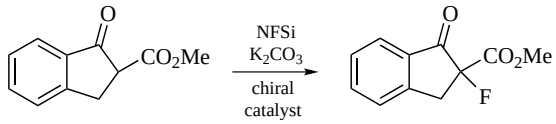
The enantioselective introduction of fluorine has been accomplished by the use of chiral imide enolates derived from Evans

oxazolidone chiral auxiliary (eq 13). This approach has been utilized to prepare α-fluoroaldehyde,[15] α-fluoroketone,[16] α-fluoroacid,[17] and 2-deoxy-2-fluoropentose derivatives.[18–20] Fluorination of β-keto amides can be used as a method to prepare 3-fluoroazetidinones.[21,22]



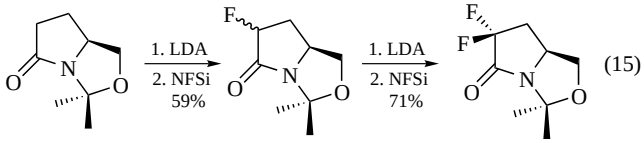
(13)

Catalytic enantioselective fluorination of β-keto esters can be accomplished with chiral quaternary ammonium salts as phase-transfer catalysts (eq 14).[23]



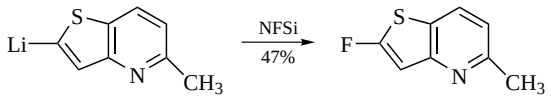
(14)

N-fluorobenzenesulfonimide also reacts with lactone and lactam enolates to afford the corresponding α-fluoro derivative.[24–27] Glutamates can be monofluorinated in the 4-position by this method.[28] Repeating the reaction sequence affords the corresponding difluorinated product (eq 15).[29]



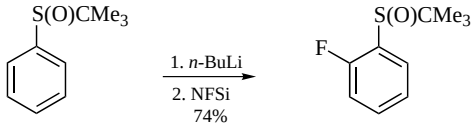
(15)

Reaction with Organolithium Reagents. The fluorination of vinyl lithium derivatives with NFSi has been demonstrated in good yields with complete retention of configuration about the double bond.[1] Phenyl lithium reacts rather poorly with *N*-fluorobenzenesulfonimide, but more complex phenyl lithium derivatives have been fluorinated to prepare fluoro- and polyfluoro-veratraldehydes as well as complex fluorinated polyaromatic compounds.[30–36] Organolithium derivatives of heterocycles have been fluorinated by reaction with NFSi at low temperature. In this manner, fluoro-pyrroles[37] and 2-fluoro-5-methylthieno[3,2-b]pyridine are prepared from their corresponding lithio-parent compounds (eq 16).[38]



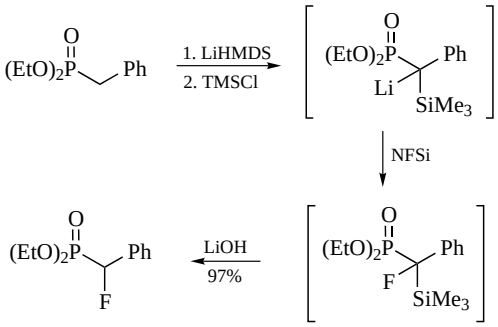
(16)

The directed ortho metalation (DoM) strategy has been used to regiospecifically fluorinate the ortho metalated aromatic and heteroaromatic substrates with *N*-fluorobenzenesulfonimide.[1,3,8,30,39] A variety of fluorinated products are available using metalation conditions appropriate for the specific directed metalation group (DMG); modest to good yields of the corresponding fluorinated material were realized with carbon-, oxygen-, and sulfur-based directing groups (eq 17).



(17)

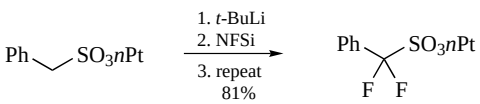
Reaction with Phosphonates. Monofluorophosphonates are prepared by low-temperature electrophilic fluorination of alkyl phosphonate anions with *N*-fluorobenzenesulfonimide in poor to modest yields.[2,40,41] This procedure is complicated by the generation of the monohalogenated product that is more acidic than the initial phosphonate, thus inducing an acid–base equilibrium that results in the formation of a mixture of starting phosphonate and the monofluoro derivative. The use of a silylated phosphonate anion avoids this complication and after desilation with mild base the monofluorophosphonates can be realized in good yields (eq 18).[42–44] Aryl α,α-difluoromethylene phosphonates can be prepared in a single step with moderate to good yields by treating benzyl phosphonates with 2.2 equiv of sodium bis(trimethylsilyl)-amide and 2.5 equiv of NFSi.[45–47]



(18)

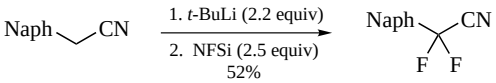
Reaction with Other Nucleophiles. Electron-rich aromatics can be fluorinated in low to modest yield by heating with *N*-fluorobenzenesulfonimide without a solvent to about 100–150 °C (eq 9).[1,48]

Regio- and stereoselective electrophilic fluorination at C19 of vitamin D-SO_2 adducts was achieved with NFSi and bulky bases.[49] Benzylic α,α-difluorosulfonates have been prepared by stepwise reaction of the corresponding benzylic sulfonate with *t*-butyl lithium and NFSi (eq 19).[46]



(19)

N-Fluorobenzenesulfonimide in conjunction with a strong base regioselectively fluorinates unsaturated nitriles on the carbon α to the cyano group. Similar chemistry can be accomplished without the presence of the double bond.[50] Benzyl nitriles have been converted to benzylic α,α-difluoro nitriles in a one-step fluorination reaction, using 2.2 equiv of *t*-butyl lithium and 2.5 equiv of NFSi (eq 20). Difluorotetrazoles can also be prepared by this methodology.[46] For the synthesis of (8*S*)-8-fluoroerythromycins, the corresponding 8,9-anhydroerythromycins 6,9-hemiketal are reacted with NFSi.[51]



(20)

Related Reagents. These include *N*-fluorobenzenedisulfonimide,[3] *N*-fluoroperfluoroalkane Sulfonimides,[4] and 2-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide.[5] For a review on electrophilic fluorinating agents, see German and Zemskov.[6] 1-Fluoro-4-hydroxy-1; 4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate).

1. Differding, E.; Ofner, H., *Synlett* **1991**, 187.
2. Differding, E.; Duthaler, R. O.; Krieger, A.; Rüegg, G. M.; Schmit, C., *Synlett* **1991**, 395.
3. Davis, F. A.; Han, W., *Tetrahedron Lett.* **1991**, *32*, 1631.
4. Singh, S.; DesMarteau, D. D.; Zuberi, S. S.; Witz, M.; Huang, H.-N., *J. Am. Chem. Soc.* **1987**, *109*, 7194.
5. Differding, E.; Rüegg, G. M.; Lang, R. W., *Tetrahedron Lett.* **1991**, *32*, 1779 and refs. cited therein.
6. *New Fluorinating Agents in Organic Synthesis*; German, L.; Zemskov, S. Eds.; Springer: Berlin, 1989.
7. Davis, F. A.; Reddy, R. E., *Tetrahedron: Asymmetry* **1994**, *5*, 955.
8. Snieckus, V.; Beaulieu, F.; Mohri, K.; Han, W.; Murphy, C. K.; Davis, F. A., *Tetrahedron Lett.* **1994**, *35*, 3465.
9. Jung, M. E.; Toyota, A., *J. Org. Chem.*, **2001**, *66*, 2624.
10. Padova, A. et al., *J. Chem. Soc., Chem. Commun.* **1995**, 661.
11. Padova, A. et al., *Tetrahedron* **1996**, *52*, 263.
12. U. S. Pat. 6,316,498 (to Nakazato, A. et al.) (2001).
13. Poss, A. J.; Shia, G. A., *Tetrahedron Lett.* **1995**, *36*, 4721.
14. Enders, D.; Faure, S.; Potthoff, M.; Runsink, J., *Synthesis* **2001**, 2307.
15. Davis, F. A.; Kasu, V. N.; Sundarababu, G.; Qi, H., *J. Org. Chem.* **1997**, *62*, 7546.
16. Davis, F. A.; Kasu, P., *Tetrahedron Lett.* **1998**, *39*, 6135.
17. Davis, F. A.; Han, W., *Tetrahedron Lett.* **1992**, *33*, 1153.
18. Davis, F. A.; Qi, H., *Tetrahedron Lett.* **1996**, *37*, 4345.
19. Siddiqui, M. A.; Marquez, V. E.; Driscoll, J. S.; Barchi, J. J., *Tetrahedron Lett.* **1994**, *35*, 3263.
20. Davis, F. A.; Qi, H.; Sundarababu, G., *Tetrahedron* **2000**, *56*, 5303.
21. Genet, J.-P. et al., *Tetrahedron Lett.* **1997**, *38*, 69.
22. Padova, A. et al., *Tetrahedron* **1996**, *52*, 263.
23. Kim, D. Y.; Park, E. J., *Org. Lett.* **2002**, *4*, 545.
24. Van Vliet, D. S.; Lee, K.-H., *Tetrahedron Lett.* **1999**, *40*, 2259.
25. McAtee, J. J.; Schinazi, R. F.; Liotta, D., *J. Org. Chem.* **1998**, *63*, 2161.
26. Dehoux, C.; Gorrichon, L.; Baltas, M., *Eur. J. Org. Chem.* **2001**, 1105.
27. Johnson, D. V.; Fischer, R.; Griengl, H., *Tetrahedron* **2000**, *56*, 9289.
28. Konas, D. W.; Coward, J. K., *J. Org. Chem.* **2001**, *66*, 8831.
29. Konas, D. W.; Coward, J. K., *Org. Lett.* **1999**, *1*, 2105.
30. Davis, F.; Han, W.; Murphy, C., *J. Org. Chem.* **1995**, *60*, 4730.
31. Zajc, B., *J. Org. Chem.* **1999**, *64*, 1902.
32. DE Pat. 42,19,281 (to Pauluth, D.).
33. Nie, J.; Kirk, K., *J. Fluorine Chem.* **1995**, *74*, 297.
34. Boger, D. L.; Brunette, S. R.; Garbaccio, R. M., *J. Org. Chem.* **2001**, *66*, 5163.
35. Tagat, J. R. et al., *J. Org. Chem.* **2002**, *67*, 1171.
36. Collman, J. P.; Zhong, M.; Boulatov, R., *J. Chem. Research (S)* **2000**, 230.
37. Barnes, K.; Hu, Y.; Hunt, D., *Synth. Commun.* **1994**, *24*, 1749.
38. EP Pat. 0,604,114 (to Labelle, M. et al.)
39. U. S. Pat. 5,670,691 (to Spangler, L. A.; Weaver, D. G.) (1997).
40. Chen, W.; Flavin, M. T.; Filler, R.; Xu, Z.-Q., *Tetrahedron Lett.* **1996**, *37*, 8975.
41. Wang, Z.; Gu, Y.; Zapata, A. J.; Hammond, G. B., *J. Fluorine Chem.* **2001**, *107*, 127.
42. Iorga, B.; Eymery, F.; Savignac, P., *Tetrahedron* **1999**, *55*, 2671.
43. Iorga, B.; Eymery, F.; Savignac, P., *Tetrahedron Lett.* **1998**, *39*, 3693.
44. Iorga, B.; Eymery, F.; Savignac, P., *Synthesis* **2000**, 576.
45. Taylor, S. D.; Dinaut, A. N.; Thadani, A. N.; Huang, Z., *Tetrahedron Lett.* **1996**, *37*, 8089.
46. Kotoris, C. C.; Chen, M.-J.; Taylor, S. D., *J. Org. Chem.* **1998**, *63*, 8052.
47. Taylor, S. D.; Kotoris, C. C.; Dinaut, A. N.; Chen, M.-J., *Tetrahedron* **1998**, *54*, 1691.
48. O'Neill, P. M.; Storr, R. C.; Park, B. K., *Tetrahedron* **1998**, *54*, 4615.
49. Shimizu, M.; Iwasaki, Y.; Ohno, A.; Yamada, S., *Chem. Pharm. Bull.* **2000**, *48*, 1484.
50. Hooper, A. M.; Beddie, D. G.; Khambay, B., *Pestic Sci.* **1999**, *55*, 486.
51. U. S. Pat. 5,552,533 (to Poss, A. J.; Shia, G. A.) (1996).

Fluorosulfuric Acid

[7789-21-1] FHO_3S (MW 100.08)
InChI = 1/FHO3S/c1-5(2,3)4/h(H,2,3,4)
InChIKey = UQSQSQZYBQSBJZ-UHFFFAOYAW

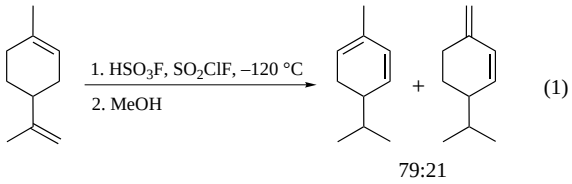
(strong Brønsted superacid[1] used as catalyst and reagent for alkylation, isomerization, rearrangement, cyclization, cycloaddition, ring-opening polymerization, and fluorosulfonation; also widely used in generation of stable carbocations)

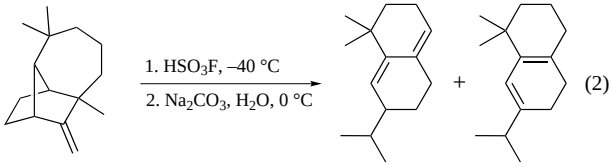
Alternate Name: fluorosulfonic acid.
Physical Data: mp −89.0 °C; bp 162.7 °C; *d* 1.743 g cm^{-3}.
Solubility: sol nitrobenzene, diethyl ether, acetic acid, ethyl acetate; insol carbon disulfide, carbon tetrachloride, chloroform. It dissolves most organic compounds that are potential proton acceptors.
Form Supplied in: colorless liquid; commercially available.
Handling, Storage, and Precautions: fluorosulfuric acid is highly toxic and corrosive and should always be handled in a fume hood with proper protection. It can be purified by distillation under anhydrous conditions using common glassware. When water is excluded, it may be handled and stored in glass containers, but containers should always be cooled before opening because HF gas pressure may have developed due to hydrolysis. For long-term laboratory storage, however, Teflon bottles are recommended.

Isomerization and Rearrangement. Many hydrocarbons, especially terpenes, rearrange readily in fluorosulfuric acid, usually at low temperatures, with the intermediacy of carbocations.[2–15] Compared to conventional acid systems, the use of HSO_3F often alters the normal course of acid-catalyzed isomerization and rearrangement, since the carbocation intermediates formed during the reactions are stabilized in the superacid system. For example, treatment of 1,8-*p*-menthadiene (limonene) with HSO_3F gave α- and β-phellandrenes (eq 1)[14] which were not obtained by other weaker acid systems.

Longifolene rearranges to isolongifolene and other tricyclic derivatives in the presence of 50% sulfuric acid/acetic acid in

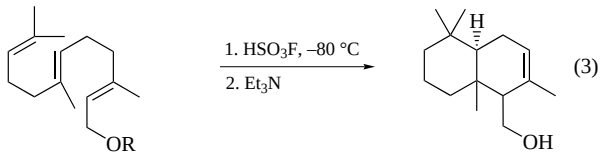
dioxane, but both longifolene and isolongifolene rearrange to a variety of bicyclic products under the catalysis of fluorosulfuric acid (eq 2).[15]



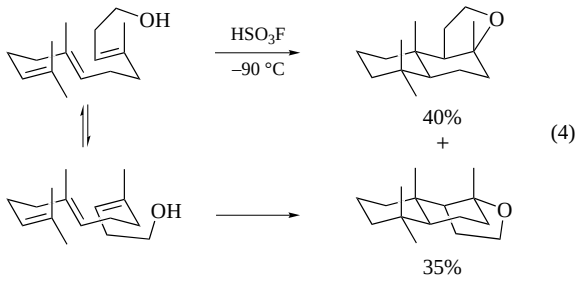


Temperature also plays an important role in determining the reaction pathway. Quenching of the reactions with bases or nucleophiles at specific temperatures can control the nature of the products.

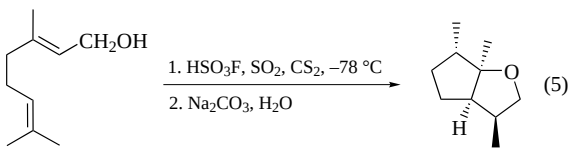
Cyclization and Ring Opening. Fluorosulfuric acid is a promising reagent in catalyzing intramolecular cyclizations at low temperature, giving better yields and higher degrees of structure selectivity compared to conventional acids. Monoterpenoids[16–21] and higher terpenoids[22–27] cyclize biomimetically by treatment with fluorosulfuric acid at low temperature (eq 3).[25]



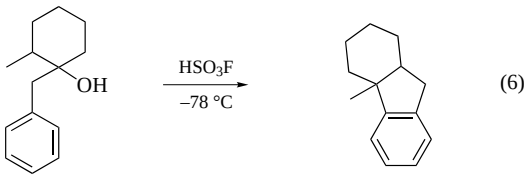
Trienols and dienols cyclize in a similar way, in the presence of an excess of fluorosulfuric acid in 2-nitropropane at −90 °C, to afford 74–87% yields of diastereoisomeric mixtures of odoriferous norlabdane oxides (eq 4).[27]



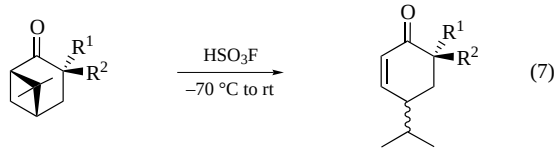
Cyclic ethers can be obtained by reacting unsaturated alcohols in fluorosulfuric acid.[28–33] Treatment of geraniol or nerol with HSO_3F at low temperature gave good yields (78 and 57%) of an iridoid ether (eq 5).[21,29b]



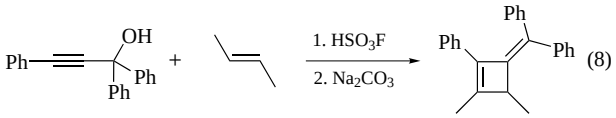
Benzyl carbinols react with fluorosulfuric acid through various reaction pathways[34–36] (rearrangement, dehydration, cyclization, ring expansion), depending on the substrate (eq 6).[34]



As opposed to cyclization, ring opening of a number of substituted nopinones occurred under fluorosulfuric acid catalysis to give 4-(2-propyl)cyclohex-2-enones (eq 7).[37] In industry, fluorosulfuric acid is used as an efficient catalyst to initiate the ring-opening polymerization of tetrahydrofuran.[38]



Cycloaddition.[39–42] Triphenylpropynol reacts in HSO_3F with alkenes or dienes to give [4 + 2] or [2 + 2] cycloaddition products (eq 8).[42]

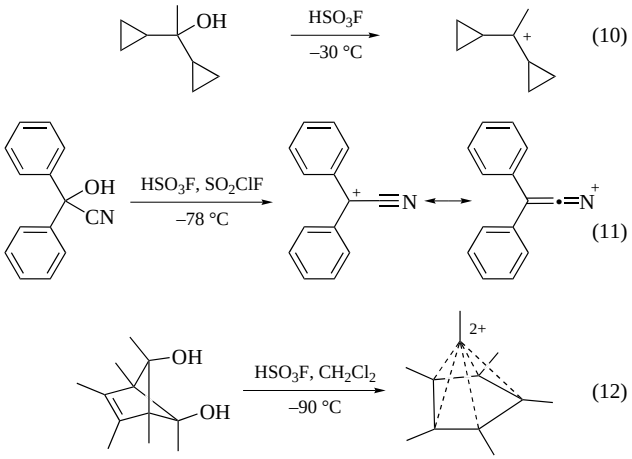


Formation of Fluorosulfates. Alkyl fluorosulfates can be prepared by addition of fluorosulfuric acid to alkenes, haloalkenes, and cyclopropanes at low temperatures with good to moderate yields (50–95%) (eq 9).[43]

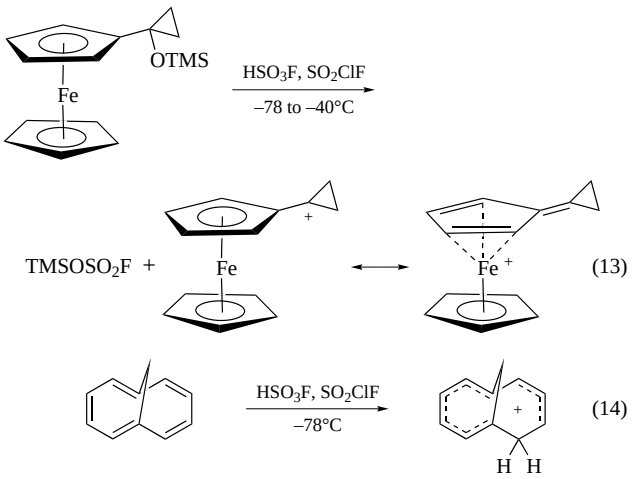
Fluorosulfonation.[44] Aromatics react with HSO_3F in the presence of variable amounts of antimony(V) fluoride to give aromatic sulfonyl fluorides and diaryl sulfones.

Generation of Stable Carbocations. Fluorosulfuric acid is the strongest known simple Brønsted acid, with an H_0 value[45] of −15.1 (compared to −12 for 100% sulfuric acid, −14.1 for trifluoromethanesulfonic acid, and −15 for absolutely anhydrous hydrogen fluoride).[46] The acidity of HSO_3F can be increased by the addition of Lewis acid fluoride. HSO_3F has low viscosity, high thermal stability, and a wide liquid range (250 °C from mp to bp). These advantageous properties make HSO_3F one of the most frequently used superacids for generating stable carbocations from the corresponding alcohols at low temperature.[1–50] Generally, neat HSO_3F or acid diluted with solvents such as SO_2, SO_2ClF, freons, and dichloromethane is suitable for the preparation of carbocations stabilized by aryl, cyclopropyl, vinyl, or other π systems. Representative examples are dicyclopropyl

carbonium ions (eq 10),[47] cyanodiarylmethyl cations (nitrenium ions) (eq 11),[48] and the pyramidal $(CMe)_6^{2+}$ dication (eq 12).[49]



An intriguing cyclopropyl cation with a ferrocene substituent has been generated from its trimethylsilyl ether by eliminating trimethylsilyl fluorosulfate (eq 13).[51] 1,6-Methano[10]annulene undergoes protonation by HSO_3F in SO_2ClF to form the corresponding arenium ion (eq 14),[52] while benzenium ion generation needs a combination of HSO_3F and SbF_5.[53]



Related Reagents. Fluorosulfuric Acid–Antimony(V) Fluoride; Hydrogen Fluoride; Hydrogen Fluoride–Antimony(V) Fluoride; Nafion–H.

1. Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley: New York, 1985.
2. Sorensen, T. S., *Acc. Chem. Res.* **1976**, *9*, 257.
3. Banthorpe, D. V.; Boullier, P. A., *J. Chem. Soc., Perkin Trans. 1* **1977**, 114.
4. Osadchii, S. A.; Polovinka, M. P.; Korchagina, D. V.; Pankrushina, N. A.; Dubovenko, Z. V.; Barkhash, V. A.; Koptyug, V. A., *Zh. Org. Khim.* **1981**, *17*, 1211.
5. Polovinka, M. P.; Osadchii, S. A.; Korchagina, D. V.; Dubovenko, Z. V.; Barkhash, V. A., *Zh. Org. Khim*. **1981**, *17*, 1223.
6. Tamarova, L. E.; Nigmatova, V. B.; Korchagina, D. V.; Gatilov, Y. V.; Bagryanskaya, I. Y.; Rybalova, T. V.; Kun, O. B.; Salenko, V. L.; Anfilogova, S. N.; Belokova, N. A.; Barkhash, V. A., *Zh. Org. Khim.* **1989**, *25*, 2321.
7. Polovinka, M. P.; Korchagina, D. V.; Lyatina, L. G.; Salnikov, G. E.; Mamatyuk, V. I.; Barkhash, V. A., *Zh. Org. Khim.* **1991**, *27*, 2107.
8. Mehta, G.; Pattnaik, N.; Kappor, S. K., *Tetrahedron Lett.* **1972**, 4947.
9. Farnum, D. G.; Kappor, S. K., *Tetrahedron Lett.* **1973**, 2385.
10. Farnum, D. G.; Mader, R. A., *J. Org. Chem.* **1977**, *42*, 214.
11. Huang, E.; Ranganayakalu, K.; Sorenson, T. S., *J. Am. Chem. Soc.* **1972**, *94*, 1780.
12. Haseltine, R. P.; Sorensen, T. S., *Can. J. Chem.* **1975**, *53*, 1067.
13. Sorensen, T. S., *Acc. Chem. Res.* **1976**, *9*, 257.
14. Bardyshev, I. I.; Barkhash, V. A.; Dubovenko, Z. V.; Lysenkov, V. I., *Zh. Org. Khim.* **1978**, *14*, 1110.
15. Farnum, D. G.; Mader, R. A.; Mehta, G., *J. Am. Chem. Soc.* **1973**, *95*, 8692.
16. Kurbanov, M.; Semenovskii, A. V.; Smit, V. A., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, *2*, 390.
17. Gavrilyuk, O. A.; Korchagina, D. V.; Bagryanskaya, I. Yu.; Gatilov, Yu. V.; Kron, A. A.; Barkhash, V. A., *Zh. Org. Khim.* **1987**, *23*, 2124.
18. Gavrilyuk, O. A.; Korchagina, D. V.; Barkhash, V. A., *Zh. Org. Khim.* **1989**, *25*, 2237.
19. Gavrilyuk, O. A.; Korchagina, D. V.; Bagryanskaya, I. Yu.; Gatilov, Yu. V.; Barkhash, V. A., *Zh. Org. Khim.* **1990**, *26*, 1360.
20. Gavrilyuk, O. A.; Korchagina, D. V.; Osadchii, S. A.; Barkhash, V. A., *Zh. Org. Khim.* **1988**, *24*, 966.
21. Banthorpe, D. V.; Boullier, P. A.; Fordham, W. D., *J. Chem. Soc., Perkin Trans. 1* **1974**, 1637.
22. Banthorpe, D. V.; Boullier, P. A., *J. Chem. Soc., Perkin Trans. 1* **1977**, 114.
23. Vlad, P. F.; Ungur, N. D.; Kolsta, M. N., *Tetrahedron* **1983**, *39*, 3947.
24. Vlad, P. F.; Ungur, N. D.; Perutskii, V. B., *Khim. Prir. Soedin.* **1986**, 514.
25. Vlad, P. F.; Ungur, N. D.; Perutskii, V. B., *Khim. Prir. Soedin.* **1986**, 793.
26. Vlad, P. F.; Ungur, N. D.; Van Hung, N., *Khim. Prir. Soedin.* **1988**, 759; 760.
27. Snowden, R. L.; Eichenberger, J.-C.; Linder, S. M.; Sonnay, P.; Vial, C.; Schulte-Elte, K. H., *J. Org. Chem.* **1992**, *57*, 955.
28. Banthorpe, D. V.; Boullier, P. A., *J. Chem. Soc., Perkin Trans. 1* **1977**, 114.
29. (a) Carr, G.; Dean, C.; Whittaker, D., *J. Chem. Soc., Perkin Trans. 2* **1988**, 351.(b) Carr, G.; Dean, C.; Whittaker, D., *J. Chem. Soc., Perkin Trans. 2* **1989**, 71.
30. Baig, M. A.; Banthorpe, D. V.; Carr, G.; Whittaker, D., *J. Chem. Soc., Perkin Trans. 2* **1989**, 1981.
31. Carr, G.; Whittaker, D., *J. Chem. Soc., Perkin Trans. 2* **1989**, 359.
32. Kelly, D. P.; Giansiracusa, J. J.; Leslie, D. R.; MacKern, I. D., *Tetrahedron Lett.* **1986**, *27*, 2311.
33. Baig, M. A.; Banthorpe, D. V.; Carr, G.; Whittaker, D., *J. Chem. Soc., Perkin Trans. 2* **1990**, 163.
34. Barrow, C. J.; Bright, S. T.; Coxon, J. M.; Steel, P. J., *J. Org. Chem.* **1989**, *54*, 2542.
35. Bright, S. T.; Coxon, J. M.; Steel, P. J., *Tetrahedron Lett.* **1989**, *30*, 5651.
36. Bright, S. T.; Coxon, J. M.; Steel, P. J., *J. Org. Chem.* **1990**, *55*, 1338.
37. Coxon, J. M.; Hydes, G. J.; Steel, P. J., *Tetrahedron* **1985**, *41*, 5213.
38. Dreyfuss, P. *Poly(tetrahydrofuran)*; Gordon and Breach: New York, 1982.
39. Pittman, C. U.; Miller, W. G., *J. Am. Chem. Soc.* **1973**, *95*, 2947.
40. Deno, N. C.; Pittman, C. U.; Turner, J. O., *J. Am. Chem. Soc.* **1965**, *87*, 2153.
41. Mayr, H.; Bäuml, E., *Tetrahedron Lett.* **1983**, *24*, 357.
42. Mayr, H.; Bäuml, E., *Tetrahedron Lett.* **1984**, *25*, 1127.
43. Olah, G. A.; Nishimura, J.; Mo, Y. K., *Synthesis* **1973**, 661.
44. (a) Baker, W.; Coates, G. E.; Glockling, F., *J. Chem. Soc.* **1951**, 1376. (b) Baker, B. R.; Cory, M., *J. Med. Chem.* **1971**, *14*, 119. (c) Tanaka, M.; Souma, Y., *J. Org. Chem.* **1992**, *57*, 3738.

45. Gillespie, R. J.; Peel, T. E., *J. Am. Chem. Soc.* **1973**, *95*, 5173.
46. Gillespie, R. J.; Liang, J., *J. Am. Chem. Soc.* **1988**, *110*, 6053.
47. Deno, N. C.; Liu, J. S.; Turner, J. O.; Lincoln, D. N.; Fruit, R. E., Jr., *J. Am. Chem. Soc.* **1965**, *87*, 3000.
48. (a) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M., *J. Am. Chem. Soc.* **1980**, *102*, 6640.(b) Krishnamurthy, V. V.; Prakash, G. K. S.; Iyer, P. S.; Olah, G. A., *J. Am. Chem. Soc.* **1986**, *108*, 1575.
49. Hogeveen, H.; Kwant, P. W., *J. Am. Chem. Soc.* **1974**, *96*, 2208.
50. Prakash, G. K. S.; Reddy, V. P.; Rasul, G.; Casanova, J.; Olah, G. A., *J. Am. Chem. Soc.* **1992**, *114*, 3076.
51. Prakash, G. K. S.; Buchholz, H.; Reddy, V. P.; de Meijere, A.; Olah, G. A., *J. Am. Chem. Soc.* **1992**, *114*, 1097.
52. Warner, P.; Winstein, S., *J. Am. Chem. Soc.* **1969**, *91*, 7785.
53. Olah, G. A.; Staral, J. S.; Asencio, G.; Liang, G.; Forsyth, D. A.; Mateescu, G. D., *J. Am. Chem. Soc.* **1978**, *100*, 6299.

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Fluorosulfuric Acid–Antimony(V) Fluoride[1]

$HSO_3F–SbF_5$

[23854-38-8] F_6HO_3SSb (MW 316.83)
InChI = 1/FHO3S.5FH.Sb/c1-5(2,3)4;;;;;;/h(H,2,3,4);5*1H;/q;;;;;;+5/p-5/fFHO3S.5F.Sb/h2H;5*1h;/q;5*-1;m/rF5Sb.FHO3S/c1-6(2,3,4)5;1-5(2,3)4/h;(H,2,3,4)/f/h;2H
InChIKey = QNDPUZFBWUBSNH-OZNPEFNQCB

(a strong conjugate Brønsted–Lewis superacid system[1] widely used for the generation of stable carbocations and as catalyst and reagent for alkylation, isomerization, rearrangement, cyclization, oxyfunctionalization, formylation, sulfonation, and fluorosulfonation)

Alternate Name: Magic Acid®.
Physical Data: HSO_3F: mp −89.0 °C; bp 162.7 °C; *d* 1.743 g cm^{-3}. SbF_5: bp 149.5 °C; *d* 2.993 g cm^{-3}.
Solubility: sol SO_2ClF, liquid SO_2; solubilizes most organic compounds that are potential proton acceptors.
Form Supplied in: colorless liquid; commercially available.
Preparative Methods: $HSO_3F–SbF_5$ is prepared by mixing fluorosulfuric acid and antimony(V) fluoride at rt under dry nitrogen or argon atmosphere. The commercially available Magic Acid is a 50:50 mol % mixture of the two components. Magic Acid diluted in fluorosulfuric acid to various extents is also available. Commercial Magic Acid generally contains some HF in the form of conjugate acid.
Handling, Storage, and Precautions: Magic Acid is highly toxic, moisture sensitive, and corrosive, and should always be handled in a fume hood with proper protection. Glass is attacked by Magic Acid very slowly when moisture is excluded. Therefore, glassware may be used for handling and carrying out reactions involving Magic Acid. Teflon containers are recommended for long-term laboratory storage of Magic Acid.

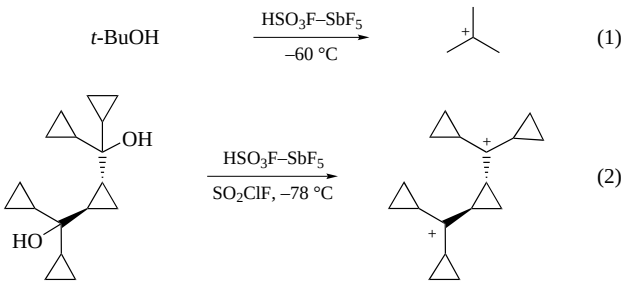
Introduction. Of all the superacids, Magic Acid is probably the most widely used medium for the study of stable long-lived carbocations and other reactive cations. The general rule is that the higher the acidity of the medium used, the more stable is the carbocation generated. The acidity of the fluorosulfuric acid–antimony pentafluoride system as a function of SbF_5 content has been studied.[2,3] The increase in acidity is very sharp at low SbF_5 concentration. The H_0 value changes from −15.1 for HSO_3F to −19.8 for a mixture containing 10% SbF_5.[2] The acidity continues up to the estimated value of H_0 = −26.5 for 90% SbF_5 content. The H_0 value for the 1:1 molar mixture of fluorosulfuric acid and antimony pentafluoride, known as Magic Acid®, is estimated to be about −23 by a dynamic NMR study.[3] The name 'Magic Acid' originated in Olah's laboratory at Case Western Reserve University in the winter of 1966 when a piece of Christmas candle was found to dissolve readily in this acid system, giving the sharp ^{1}H NMR spectrum of the *t*-butyl cation, a phenomenon considered by the research student involved to be 'magic'.[1] A major reason for the wide application of Magic Acid compared with other superacid systems, besides its very high acidity, is probably the large temperature range in which it can be used. In the liquid state, it can be studied at temperatures as low as −160 °C (acid diluted with SO_2F_2 and SO_2ClF) and as high as 150 °C (neat acid).

Magic Acid has been employed as a high acidity medium for isomerization/rearrangement, alkylation, cyclization, carboxylation, formylation, oxyfunctionalization, and related reactions. It also serves as a fluorosulfonating/sulfonating agent for aromatics.

Generation of Stable Carbocations. Thanks to its high acidity, Magic Acid can be used for the generation of such reactive carbocations as the *t*-butyl cation and other alkyl cations, while fluorosulfuric acid itself is suitable only for the generation of more stable cations such as aryl- or cyclopropyl-stabilized carbocations.

Carbocations and carbodications have been generated from a variety of precursors in Magic Acid systems.[4]

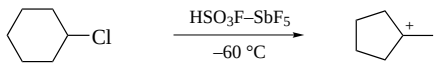
Carbocation Generation from Tertiary and Secondary Alcohols.[5–11] A wide variety of aliphatic tertiary and secondary alcohols can be ionized to the corresponding alkyl cations by using Magic Acid. Formation of the *t*-butyl cation (eq 1)[5] and a cyclopropyl-stabilized dication (eq 2)[6] are representative examples. Primary (and some secondary) alcohols are protonated only at temperatures lower than −60 °C.[7] At more elevated temperatures they may cleave to give the corresponding carbocations, which, however, immediately rearrange to the more stable tertiary cations.[8,9]



Similar to alcohols, aliphatic ethers,[12] thiols,[13] and sulfides are also protonated on oxygen or sulfur, respectively, at −60 °C in

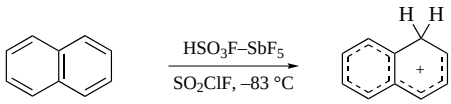
Magic Acid; carbocations are subsequently formed upon raising the temperature. Protonated sulfides, excluding tertiary alkyl, are resistant to cleavage up to +70 °C.[13]

Carbocation Generation from Alkyl Halides. Alkyl chlorides, fluorides, and bromides are convenient and frequently used precursors for generation of alkyl cations in HSO_3F–SbF_5 systems.[14] It should be noted, however, that the HSO_3F–SbF_5 system is less suitable than SbF_5 for the generation of alkyl, especially secondary alkyl, cations from the corresponding alkyl halides. Ionization of cyclohexyl chloride in Magic Acid is accompanied by isomerization, yielding the 1-methyl-1-cyclopentyl cation (eq 3).[8]



(3)

Carbocation Generation from Unsaturated Hydrocarbons. Carbocations can be generated by protonation of unsaturated hydrocarbons such as alkenes and cycloalkenes,[8,11] cyclopentadienes,[15] benzenes and naphthalenes (eq 4),[16] pyrenes and cyclophanes,[17] unsaturated heterocycles,[18] and their derivatives with carbon–heteroatom multiple bonds,[1] including carbonyl and nitrile compounds and diazoalkanes (eq 5).[19] Compounds with two sites for protonation may undergo diprotonation to give dications in Magic Acid (eq 6).[15a]



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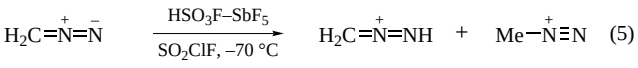

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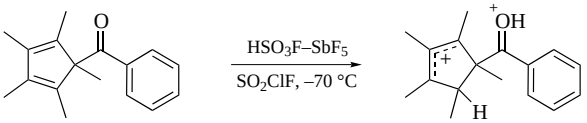
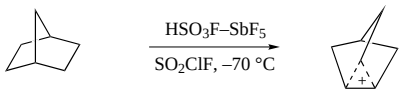


(6)

Carbocation Generation from Saturated Hydrocarbons. Magic Acid, as a strong superacid, can abstract hydride from saturated alkanes, including straight-chain alkanes as well as branched and cyclic alkanes, at −125 to 25 °C to give alkyl cations.[6,20] For example, the 2-norbornyl cation is formed through protolytic ionization by dissolving norbornane in Magic Acid (eq 7).[20b]



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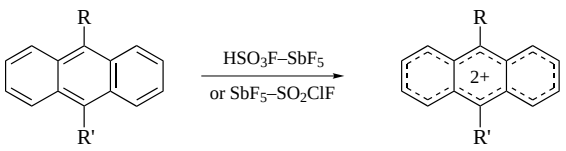
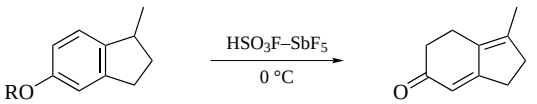
Carbocation Generation by Oxidation. Oxidation of polycyclic arenes such as naphthacene and 1,2-benzanthracene (eq 8)[21] gives arene dications.



(8)

Isomerization and Rearrangement. HSO_3F–SbF_5 is frequently used as a catalyst for the isomerization and rearrangement of terpenoids. The extremely high acidity of HSO_3F–SbF_5 allows the reaction to be carried out at temperatures as low as −100 °C and with improved selectivity.

In superacid, i.e. HSO_3F–SbF_5 or HF–SbF_5 systems, bicyclic phenols are isomerized to dienones in good yields (eq 9).[22] This is an unconventional isomerization process, in which the phenols lose their aromaticity to form nonaromatic dienones. Similar phenol-to-dienone isomerization of estrones occurs with HSO_3F–SbF_5 as catalyst, accompanied by major dehydrogenation products (eq 10).[23]



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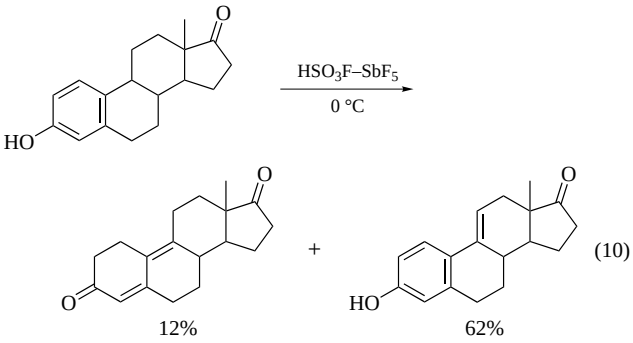
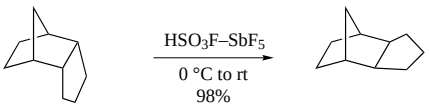


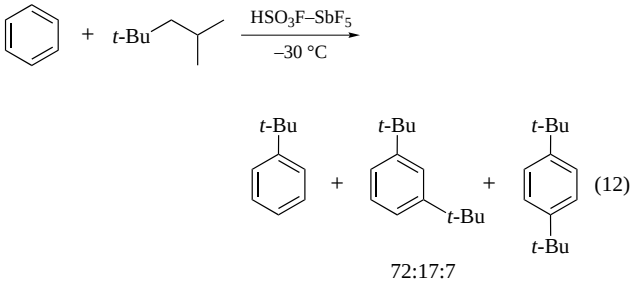
(10)

endo-Trimethylenenorbornane isomerizes to its *exo* isomer in quantitative yield at 0 °C under HSO_3F–SbF_5 catalysis (eq 11).[24] The isomerization will proceed further to adamantane when excess superacid is used (HSO_3F–SbF_5:substrate ratio = 1:3). For the rearrangement of trimethylenenorbornane to adamantane, HSO_3F–SbF_5 is, however, less efficient than CF_3SO_3H–SbF_5 or CF_3SO_3H–$B(OSO_2CF_3)_3$.[25]



(11)

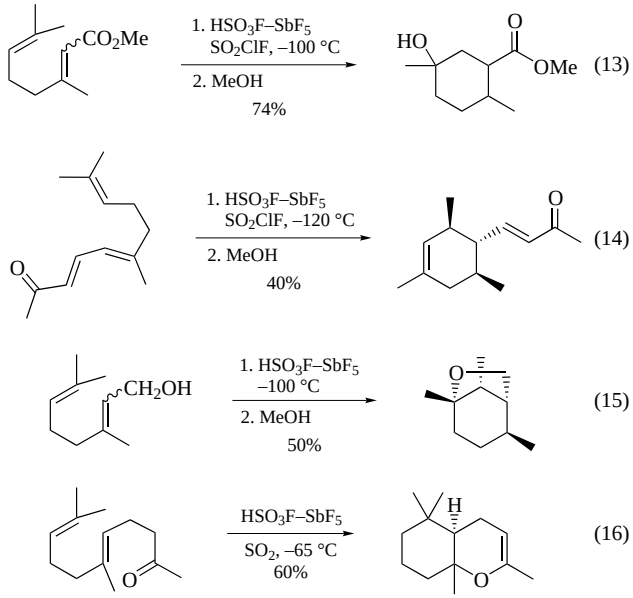
Alkylation. Benzene, alkylbenzenes, and halobenzenes undergo alkylation with 2,2,4-trimethylpentane in the presence of HSO_3F–SbF_5 at temperatures as low as −30 °C with good selectivity (eq 12).[26]



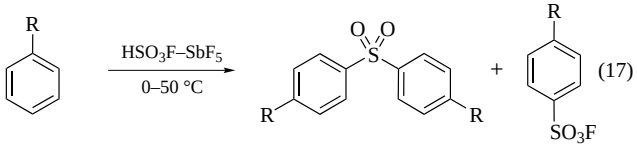
(12)

Cyclization. HSO_3F–SbF_5 has been used as a high-acidity catalyst for the cyclization of acyclic isoprenoids at low temperatures. The reaction course and products of the cationic cyclization

depend on the acidity of the catalyst and the structural differences in the substrates. Structural changes may also lead to dramatic changes in the reaction course and products. While geranate esters (eq 13)[27] and pseudoionones (eq 14)[28] are cyclized to monocyclic derivatives, geraniol or nerol (eq 15)[29] and geranylacetone (eq 16)[30] give bicyclic ethers.

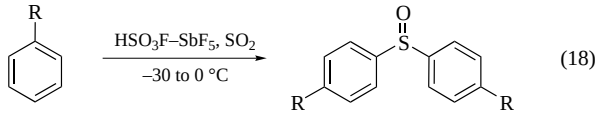


Sulfonation and Fluorosulfonation. Aromatic compounds react with HSO_3F to give arenesulfonyl fluorides.[31] When the reactions are carried out in the presence of variable amounts of SbF_5, significant amounts of diaryl sulfones are obtained (eq 17).[32] In this example, the yields of arenesulfonyl fluorides decreased with increasing amounts of SbF_5. In contrast, the yields of diaryl sulfones first increased and then decreased with increasing amounts of SbF_5. The highest yield of diphenyl sulfone was obtained when the molar ratio of SbF_5:benzene was 1:1.5. Diaryl sulfones were also obtained in high yield from toluene, xylenes, and 1,2,4-trimethylbenzene under similar conditions. Sulfonation of fluoro-, chloro-, and bromobenzenes required higher molar ratios of SbF_5:arene (1:3.5) to obtain good yields of the corresponding diaryl sulfones.



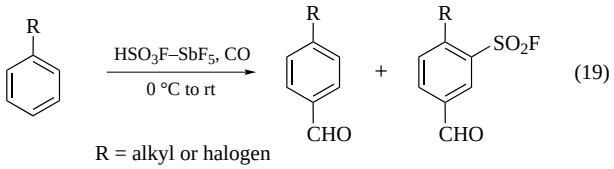
R = H	94%	4%
R = Me	95%	1%
R = F	83%	0%

Formation of Aromatic Sulfoxides. By treatment with HSO_3F–SbF_5 (1:1) and sulfur dioxide, alkylbenzenes, halobenzenes, and alkylhalobenzenes were converted to their corresponding diaryl sulfoxides along with small amounts of diaryl sulfides as minor products (eq 18).[33] In the absence of SO_2, aryl sulfone formation is the dominant process, although sulfoxide is also formed. Unsymmetrical (mixed) sulfoxides can be prepared by addition of one molar equivalent of an arene to the solution of the second arene and Magic Acid–SO_2 in Freon at low temperatures.



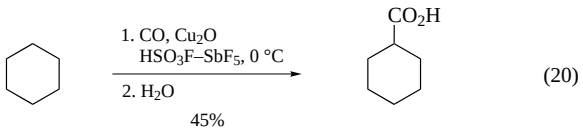
R = Me, 87%; F, 55%

Formylation and Carboxylation. Formylation of aromatic compounds such as benzene, toluene, xylenes, mesitylene, indan, tetralin, and halobenzenes is achieved in HSO_3F–SbF_5 under atmospheric CO pressure at 0 °C (eq 19).[34] However, in the cases of alkylbenzenes, both formylation and sulfonation took place under these reaction conditions to give alkylbenzaldehydes and formylalkylbenzenesulfonyl fluorides, as well as small amounts of alkylbenzenesulfonyl fluorides and bis(alkylphenyl) sulfones. With benzene and halobenzenes, because of their lower reactivity only aldehydes were produced.

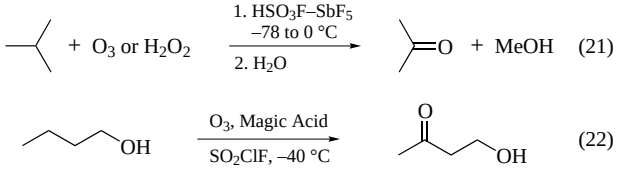


R = alkyl or halogen

Saturated hydrocarbons, including branched and unbranched chain alkanes as well as cycloalkanes, react with carbon monoxide in the presence of copper(I) oxide in HSO_3F–SbF_5 to afford tertiary and secondary carboxylic acids in high yield (eq 20).[35] The reaction proceeds at 0 °C under 1 atm CO. In some cases the reaction involves cleavage of C–C bonds and isomerization of the intermediate carbocations.

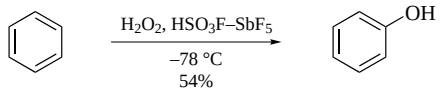


Oxyfunctionalization of Hydrocarbons. When treated with ozone[36] or hydrogen peroxide (98%)[37,38] under Magic Acid catalysis, alkanes, including methane, ethane, butanes, and higher alkanes as well as haloalkanes,[39] undergo electrophilic oxygenation followed by carbon-to-oxygen alkyl group migration giving, via alkoxycarbenium ions, ketones and alcohols (eq 21). Aliphatic alcohols, ketones, and aldehydes react with ozone in Magic Acid solution to give bifunctional oxygenated derivatives such as diketones, hydroxyl ketones, and glycols (eq 22).[40] The relative reactivity of σ-bonds in alkanes with protonated ozone was found to be $R_3C–H > R_2(H)C–H > R(H_2)C–H > C–C$.[36]

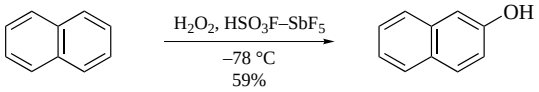


Aromatic compounds such as benzene, alkylbenzenes, and halobenzenes can be directly oxygenated with hydrogen

peroxide in Magic Acid or other superacids, giving phenols (eq 23).[41] The phenols formed are protonated by the superacids and thus are deactivated against further electrophilic attack or oxidation. When naphthalene was treated with hydrogen peroxide in Magic Acid at −78 °C, 2-naphthol was obtained (92% regioselectivity) along with small amounts of dihydroxynaphthalenes (eq 24).[42] Unlike phenol derivatives, naphthols can be further hydroxylated with hydrogen peroxide in superacid systems to dihydroxynaphthalenes, since the unprotonated ring of the protonated naphthols can still be attacked by the electrophilic hydroxylating agent.

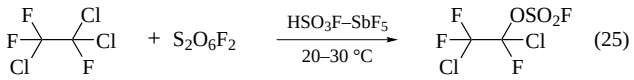


(23)



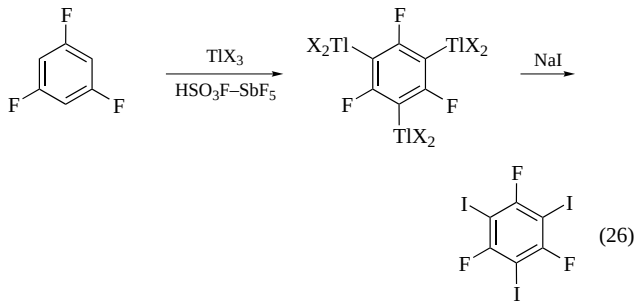
(24)

Miscellaneous Reactions. In the presence of HSO_3F–SbF_5, peroxydisulfuryl difluoride ($S_2O_6F_2$) reacts smoothly with 1,1,2-trichlorotrifluoroethane at rt to give 1,2-dichlorotrifluoroethyl fluorosulfate (eq 25).[43] $S_2O_6F_2$ alone does not react with 1,1,2-trichlorotrifluoroethane even at 150 °C, while in the presence of HSO_3F the reaction occurs only at temperatures higher than 150 °C.



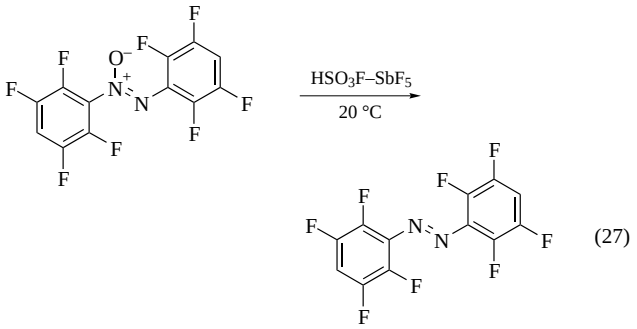
(25)

Polyfluoroarenes, such as *m*-$H_2C_6F_4$, *m*-$O_2NC_6F_4H$, *m*- and *p*-BrC_6F_4H, (*p*-$HC_6F_4)_2$, C_6F_5H, 1,3,5-$F_3C_6H_3$, and *m*-$FSO_2C_6F_4H$, have been thallated by thallium(III) trifluoroacetate in HSO_3F–SbF_5. The thallated products can be converted to polyfluoroiodoarenes by treatment with aqueous sodium iodide (eq 26).[44]



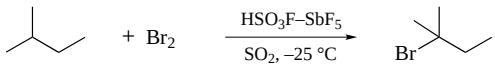
(26)

Although HSO_3F–SbF_5 is known to be a strong oxidizing system, it has been reported that octafluoroazoxybenzene was reduced by HSO_3F–SbF_5 at 20 °C to octafluoroazobenzene in quantitative yield (eq 27).[45] The mechanism of the process is still unclear.



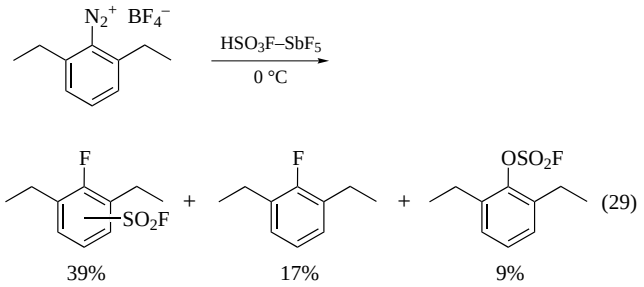
(27)

Isoalkanes are brominated by Br_2 in HSO_3F–SbF_5 to yield mono-, di-, and tribromoalkanes (eq 28).[46] Cleavage of C–C bonds occurs when isooctane is reacted under similar conditions, leading to butyl bromides.



(28)

Fluorinative dediazoniation of an arenediazonium salt occurred at 0 °C in Magic Acid (eq 29)[47] however, fluorosulfonation accompanied the dediazoniation.



(29)

Related Reagents. Antimony(V) Fluoride; Fluorosulfuric Acid; Hydrogen Fluoride; Hydrogen Fluoride–Antimony(V) Fluoride.

1. Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley: New York, 1985.
2. Gillespie, R. J.; Peel, T. E., *J. Am. Chem. Soc.* **1973**, *95*, 5173.
3. Gold, V.; Laali, K.; Morris, K. P.; Zdunek, L. Z., *J. Chem. Soc., Chem. Commun.* **1981**, 769.
4. For reviews, see(a) Hanack, M., *Methoden Org. Chem. (Houen-Weyl)* **1990**, *E19C*. (b) Prakash, G. K. S.; Rawdah, T. N.; Olah, G. A., *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 390.
5. Olah, G. A.; Comisarow, M. B.; Cupas, C. A.; Pittman, C. U., Jr., *J. Am. Chem. Soc.* **1965**, *87*, 2998.
6. (a) Prakash, G. K. S.; Fung, A. P.; Rawdah, T. N.; Olah, G. A., *J. Am. Chem. Soc.* **1985**, *107*, 2920. (b) Olah, G. A.; Reddy, V. P.; Lee, G.; Casanova, J.; Prakash, G. K. S., *J. Org. Chem.* **1993**, *58*, 1639.
7. Olah, G. A.; Namanworth, E., *J. Am. Chem. Soc.* **1966**, *88*, 5327.
8. (a) Olah, G. A.; Bollinger, J. M.; Cupas, C. A.; Lucas, J., *J. Am. Chem. Soc.* **1967**, *89*, 2692. (b) Olah, G. A.; Prakash, G. K. S.; Sommer, J., *Science* **1979**, *206*, 13.
9. Olah, G. A.; Sommer, J., *J. Am. Chem. Soc.* **1968**, *90*, 927.
10. (a) Olah, G. A.; Pittman, C. U., Jr.; Namanworth, E.; Comisarow, M. B., *J. Am. Chem. Soc.* **1966**, *88*, 5571. (b) Sorensen, T. S.; Rajeswari, K., *J. Am. Chem. Soc.* **1971**, *93*, 4222.
11. Hogeveen, H.; Kwant, P. W., *J. Am. Chem. Soc.* **1974**, *96*, 2208.

12. Olah, G. A.; O'Brien, D. H., *J. Am. Chem. Soc.* **1967**, *89*, 1725.
13. Olah, G. A.; O'Brien, D. H.; Pittman, C. U., Jr., *J. Am. Chem. Soc.* **1967**, *89*, 2996.
14. (a) Olah, G. A.; White, A. M., *J. Am. Chem. Soc.* **1969**, *91*, 5801. (b) Olah, G. A.; Donovan, D. J., *J. Am. Chem. Soc.* **1977**, *99*, 5026.
15. (a) Childs, R. F.; Zeya, M., *Can. J. Chem.* **1975**, *53*, 3425. (b) Olah, G. A.; Prakash, G. K. S.; Liang, G., *J. Org. Chem.* **1977**, *42*, 661. (c) Olah, G. A.; Pittman, C. U., Jr.; Sorensen, T. S., *J. Am. Chem. Soc.* **1966**, *88*, 2331.
16. Olah, G. A.; Mateescu, G. D.; Mo, Y. K., *J. Am. Chem. Soc.* **1973**, *95*, 1865.
17. (a) Prakash, G. K. S.; Rawdah, T. N.; Olah, G. A., *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 390. (b) Laali, K. K.; Hansen, P. E., *J. Org. Chem.* **1991**, *56*, 6795. (c) Laali, K. K.; Gelerinter, E.; Filler, R., *J. Fluorine Chem.* **1991**, *53*, 107.
18. Yoshino, A.; Takahashi, K.; Sone, T., *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3228.
19. (a) McGarrity, J. F.; Cox, D. P., *J. Am. Chem. Soc.* **1983**, *105*, 3961. (b) Olah, G. A.; White, A. M., *J. Am. Chem. Soc.* **1968**, *90*, 6087. (c) Olah, G. A.; O'Brien, D. H.; Calin, M., *J. Am. Chem. Soc.* **1967**, *89*, 3582. (d) Olah, G. A.; White, A. M.; O'Brien, D. H., *Chem. Rev.* **1970**, *70*, 561. (e) Olah, G. A.; Nakajima, T.; Prakash, G. K. S., *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 811.
20. (a) Olah, G. A.; Lukas, J., *J. Am. Chem. Soc.* **1967**, *89*, 4739. (b) Olah, G. A.; Lukas, J., *J. Am. Chem. Soc.* **1968**, *90*, 933.
21. (a) van der Lugt, W. T. A. M.; Buck, H. M.; Oosterhoff, L. J., *Tetrahedron* **1968**, *24*, 4941. (b) Olah, G. A.; Singh, B. P., *J. Org. Chem.* **1983**, *48*, 4830. (c) Prakash, G. K. S.; Fessner, W.-D.; Olah, G. A., *J. Am. Chem. Soc.* **1989**, *111*, 746.
22. Coustard, J. M.; Jacquesy, J. C., *Tetrahedron Lett.* **1972**, 1341.
23. Gesson, J. P.; Jacquesy, J. C.; Jacquesy, R., *Tetrahedron Lett.* **1971**, 4733.
24. Jacquesy, J. C.; Jacquesy, R.; Moreau, S.; Patoiseau, J. F., *J. Chem. Soc., Chem. Commun.* **1973**, 785.
25. Olah, G. A.; Farooq, O., *J. Org. Chem.* **1986**, *51*, 5410.
26. Kroeger, C. F.; Miethchen, R.; Mann, H.; Hoffmann, K.; Wiechert, K., *J. Prakt. Chem.* **1978**, *320*, 881.
27. Gavrilyuk, O. A.; Korchagina, D. V.; Bagryanskaya, I. Yu.; Gatilov, Yu. V.; Kron, A. A.; Barkhash, V. A., *Zh. Org. Khim.* **1987**, 2124.
28. Gavrilyuk, O. A.; Korchagina, D. V.; Gatilov, Yu. V.; Mamatyuk, S. A.; Osadchii, S. A.; Fisher, E. A.; Dubovenko, Z. V.; Barkhash, V. A., *Zh. Org. Khim.* **1987**, 457.
29. Gavrilyuk, O. A.; Korchagina, D. V.; Barkhash, V. A., *Zh. Org. Khim.* **1989**, 2237.
30. Mustafaeva, M. T.; Smit, V. A.; Semenovskii, A. V.; Kucherov, V. F., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, 1151.
31. (a) Renoll, M. W., *J. Am. Chem. Soc.* **1942**, *64*, 1489. (b) Baker, W.; Coates, G. E.; Glockling, F., *J. Chem. Soc.* **1951**, 1376. (c) Baker, B. R.; Cory, M., *J. Med. Chem.* **1971**, *14*, 119.
32. Tanaka, M.; Souma, Y., *J. Org. Chem.* **1992**, *57*, 3738.
33. Laali, K. K.; Nagvekar, D. S., *J. Org. Chem.* **1991**, *56*, 1867.
34. Tanaka, M.; Iyoda, J.; Souma, Y., *J. Org. Chem.* **1992**, *57*, 2677.
35. Souma, Y.; Sano, H., *Bull. Chem. Soc. Jpn.* **1976**, 3335.
36. Olah, G. A.; Yoneda, N.; Parker, D. G., *J. Am. Chem. Soc.* **1976**, *98*, 5261.
37. Olah, G. A.; Yoneda, N.; Parker, D. G., *J. Am. Chem. Soc.* **1977**, *99*, 483.
38. Yoneda, N.; Olah, G. A., *J. Am. Chem. Soc.* **1977**, *99*, 3113.
39. Olah, G. A.; Yoneda, N.; Parker, D. G., *J. Am. Chem. Soc.* **1976**, *98*, 2251.
40. Olah, G. A.; Yoneda, N.; Ohnishi, R., *J. Am. Chem. Soc.* **1976**, *98*, 7341.
41. Olah, G. A.; Ohnishi, R., *J. Org. Chem.* **1978**, *43*, 865.
42. Olah, G. A.; Keumi, T.; Lecoq, J. C.; Fung, A. P.; Olah, J. A., *J. Org. Chem.* **1991**, *56*, 6148.
43. Fokin, A. V.; Studnev, Y. N.; Rapkin, A. I.; Matveenko, V. I., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 715.
44. Deacon, G. B.; Smith, R. N. M., *Aust. J. Chem.* **1982**, 1587.
45. Furin, G. G.; Andreevskaya, O. I.; Rezvukhin, A. I.; Yakobson, G. G., *J. Fluorine Chem.* **1985**, *28*, 1.
46. Halpern, Y., *Isr. J. Chem.* **1976**, *13*, 99.
47. Laali, K.; Szele, I.; Zollinger, H., *Helv. Chim. Acta* **1983**, 1737.

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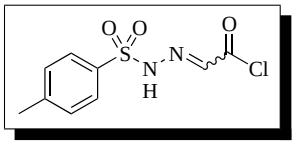
University of Southern California, Los Angeles, CA, USA

G

Glyoxylyl Chloride *p*-Toluenesulfonylhydrazone[1]



[14661-69-9] $C_9H_{10}ClN_2O_3S$ (MW 261.73)
InChI = 1/C9H9ClN2O3S/c1-7-2-4-8(5-3-7)16(14,15)12-11-6-9(10)13/h2-6,12H,1H3
InChIKey = HQXCAVDYGRHYMF-UHFFFAOYAK

(synthesis of α-diazo esters and amides[2])

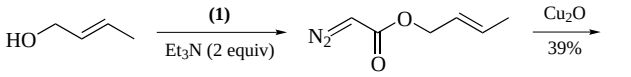
Physical Data: mp 103–110 °C (dec).
Solubility: sol methylene chloride, chloroform, THF, and warm benzene.
Preparative Method: not commercially available; however, it can be prepared readily by the reaction of *p*-toluenesulfonylhydrazide and glyoxylic acid.[2]
Handling, Storage, and Precaution: anhydrous conditions are required; it is advisable to prepare the reagent freshly prior to use.

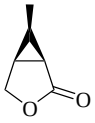
Original Commentary

Ioannis Grapsas & Shahriar Mobashery
Wayne State University, Detroit, MI, USA

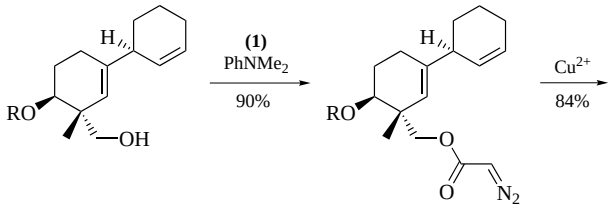
Introduction. Glyoxylyl chloride *p*-toluenesulfonylhydrazone (**1**) is a versatile reagent for the synthesis of diazoacetyl esters and amides, which upon heating in the presence of a metal catalysts or irradiation generate reactive carbene intermediates.[1] Compound (**1**) undergoes reaction with alcohols to give the corresponding α-diazoacetyl esters under mild basic conditions. Typically, 2 equiv of triethylamine are used in this reaction (eq 1). However, sulfinate species have been reported to contaminate the product.[1b] Corey and Meyers have shown that the formation of this undesired byproduct can be largely circumvented by the use of *N*,*N*-dimethylaniline instead of Et_3N (eq 2).[1b]

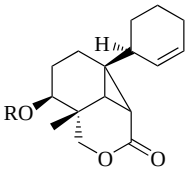
The existing alternative preparative methods for the α-diazo esters, such as diazotization of glycine esters,[3] pyrolysis of *N*-acyl-*N*-nitrosoglycine esters,[4] base-catalyzed cleavage of α-diazo-β-ketoacetates,[5] reactions of alkoxycarbonylmethylenephosphoranes with arenesulfonyl azides,[6] or acid-catalyzed decomposition of acetic esters with aryltriazene substituents,[7] all suffer from the disadvantage of being multistep synthetic procedures, and that at times harsh conditions (high temperature, strong acid or base) must be employed.





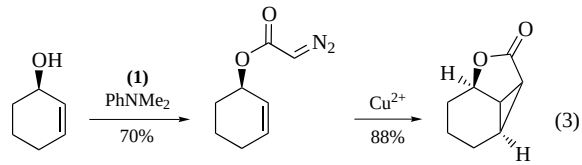
(1)



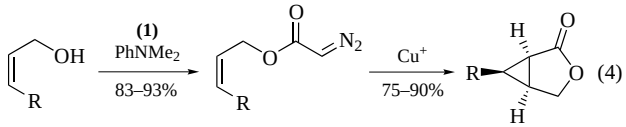


(2)

Intramolecular Cyclopropanation. The resultant α-diazoacetyl ester from the reaction of (**1**) and an unsaturated alcohol undergoes cyclization in the presence of transition metals to give cyclopropyl derivatives (eq 3, 4); the reaction proceeds via an intermediary carbene species.[1] Owing to the geometric constraints of the intramolecular cyclopropanation, the substituents and the product acquire all-*cis* configurations.[2] This is in contrast to the bimolecular cyclopropanation, which is unable to achieve sterochemical control, resulting in mixtures of products.



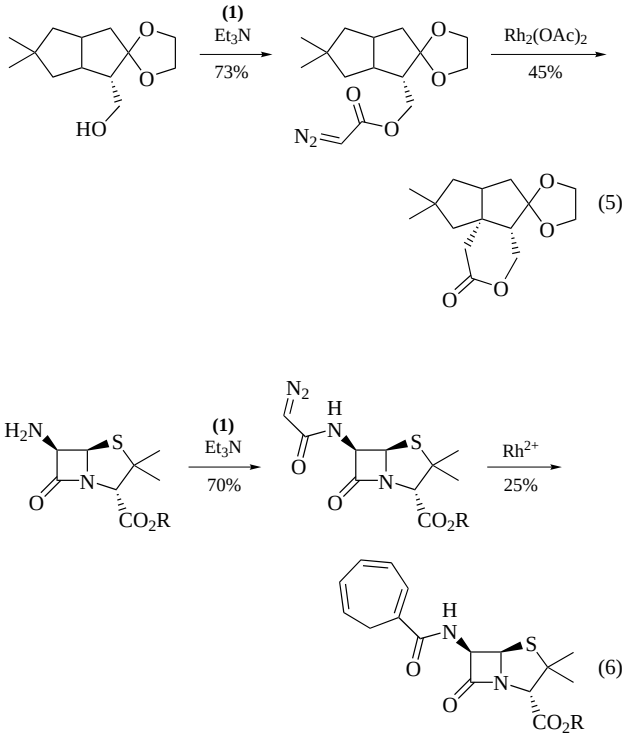
(3)

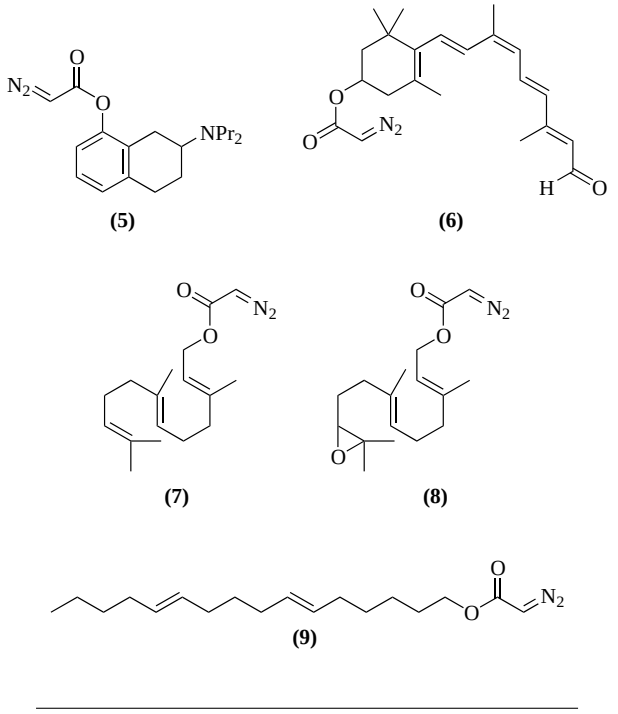


(4)

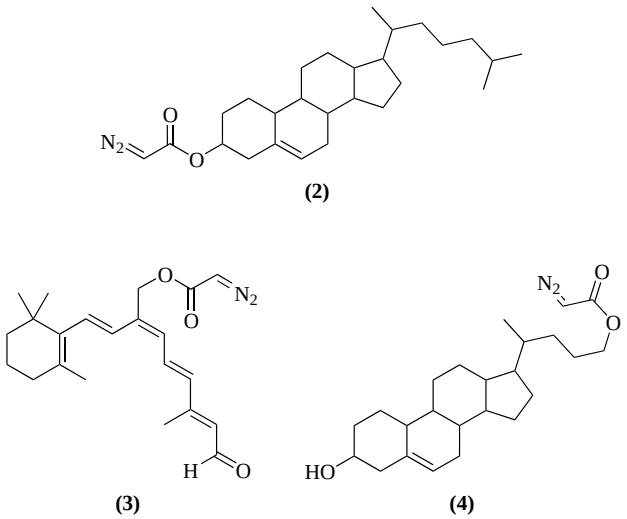
C–H and C–C Carbene Insertion Reactions. Intramolecular carbene insertion at an unactivated bridgehead site is reported from an α-diazoacetyl ester precursor (eq 5).[8]

Decomposition of 6-(α-diazoacetamide)penicillanate in the presence of copper(II) or rhodium(II) in refluxing benzene resulted in the formation of a cycloheptatriene moiety (eq 6).[9]





Photoaffinity Labels. As an application of the carbene insertion reaction in structural studies of macrobiomolecules, radioactively labeled α-diazo esters have been used as photoaffinity labels.[10] Such esters are designed to bind specific targetted biological receptors (e.g. enzymes, membrane receptor proteins, nucleic acids, etc.). Photolysis of the complex generates the high-energy carbene species that inserts into C–H or X–H (X = a hetero atom) bonds in the receptor molecule readily at ambient temperature. In the absence of a facile insertion reaction, the resultant unquenched carbene may undergo Wolff rearrangement, thereby wasting a percentage of the reactive species for photoaffinity labeling.[11] The structures of a number of such biologically active molecules are shown in (**2**)–(**9**); these molecules are prepared typically by the reaction of reagent (**1**) with the corresponding alcohols in moderate to good yields.[10]



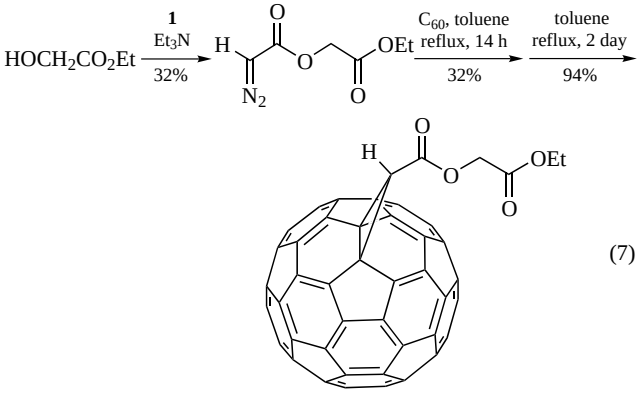
First Update

Mingyi Liao & Jianbo Wang
Peking University, Beijing, China

Glyoxylyl chloride *p*-toluenesulfonylhydrazone (**1**) continues to be a powerful reagent for the synthesis of diazoacetyl esters and amides. In most cases, the diazoacetyl esters and amides, which can be obtained from the reaction of (**1**) with corresponding alcohols or amines, are subjected to the catalysis with transition metal complex. A series of synthetically useful transformations, typically cyclopropanation, C–H insertion and ylide formation, can occur in these catalytic reactions. There are several excellent reviews in this area that have been published during the past decade.[12]

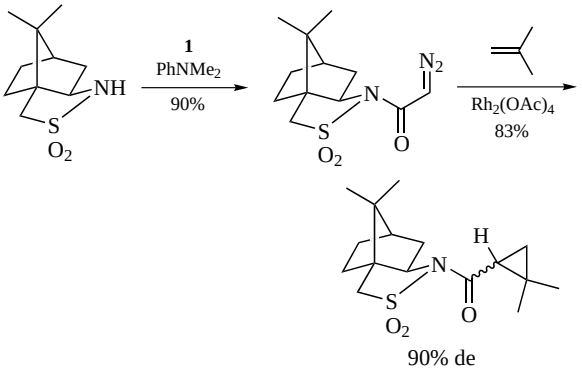
Intermolecular Cyclopropanation. Transition metal catalytic decomposition of diazocarbonyl compounds in the presence of alkenes provides a facile and powerful means for constructing cyclopropanes. Due to the high regio- and stereoselectivities, intramolecular cyclopropanation has received considerable attention during the past several decades.[13] Intramolecular cyclopropanation has recently mainly focused on enantioselective reactions. Thus, an allylic alcohol reacts with compound (**1**) to give the corresponding diazoester. The allylic diazoester is then decomposed in the presence of a chiral catalyst to afford the cyclopropyl derivative in high enantiomeric excess. In some cases the resultant cyclopropyl derivatives were further transformed into useful molecules such as conformationally restricted peptide isosteres.[13a,c–e,h]

Intermolecular cyclopropanation of α-diazo carbonyl compounds is also reported.[14] For example, ethyl glycolate undergoes reaction with compound (**1**) to give the diazo diester, which was subsequently reacted with C_{60} to form a methanofullerene (eq 7).[14]



(7)

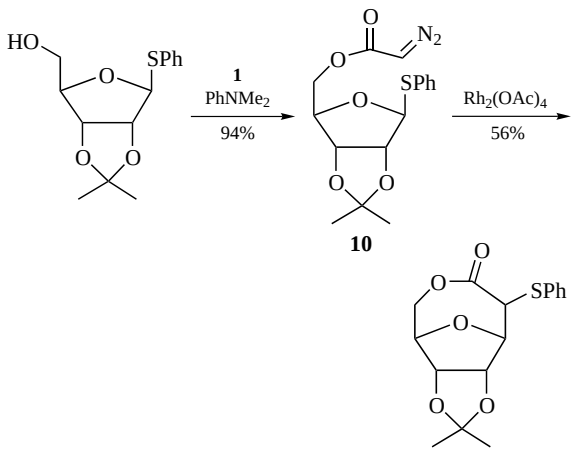
Haddad and Galili have reported a highly diastereoselective cyclopropanation of alkenes with the Oppolzer's sultam as chiral auxiliary (eq 8).[14b] Reaction of (**1**) with the sultam gives a high yield of the corresponding diazoacetyl amide.



(8)

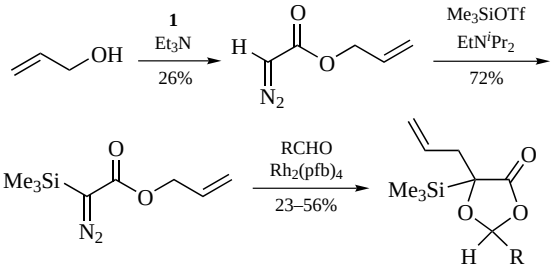
90% de

Ylide Reaction. Ylide formation in catalytic carbene transfer reactions has attracted considerable attention in the past decade. The ylide can be easily generated from a metal carbene and a Lewis base, such as carbonyl compound or sulfide. The highly reactive ylide then proceeds to undergo further reactions. For example, diazoacetic ester (**10**) is prepared from *β*-phenylthio-2,3-*O*-isopropylidene-D-ribofuranose and compound (**1**). Decomposition of (**10**) in refluxing benzene containing rhodium(II) acetate results in lactone (**11**) via an eight-membered cyclic sulfonium ylide intermediate (eq 9).[15]



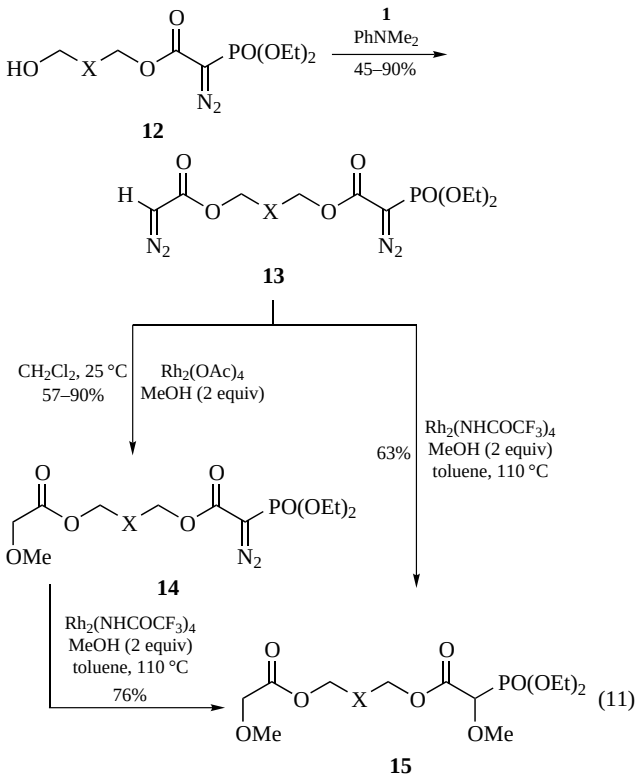
(9)

A carbonyl ylide reaction is demonstrated in eq 10. The diazoester from reaction of compound (**1**) and allyl alcohol is subsequently treated with Me_3SiOTf. The unsaturated silyldiazoester reacts with various aldehydes or acetone catalyzed by rhodium(II) perfluorobutyrate to afford 1,3-dioxolan-4-ones in moderate yields via carbonyl ylide intermediates (eq 10).[16]



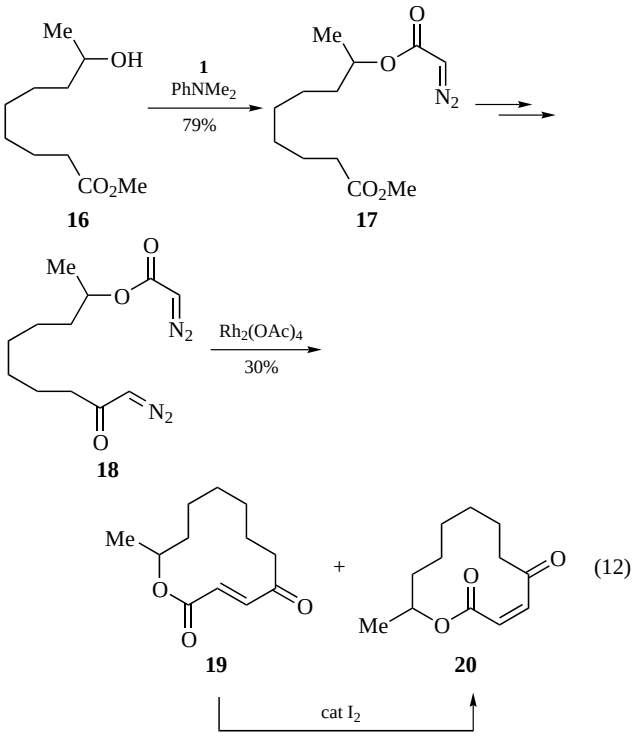
(10)

O–H Insertion Reaction. Metal carbenes easily react with hydroxyl groups to afford O–H insertion products. An example is shown in eq 11. Diazo alcohol (**12**) readily reacts with reagent (**1**) to give the corresponding bis(diazo) compound (**13**). (**13**) bears two differently substituted diazo groups. When rhodium(II) acetate is used as the catalyst, the more reactive diazo system suffers selective O–H insertion to afford the monodiazo compound (**14**). Treatment of compound (**14**) with methanol and the more active rhodium(II) trifluoroacetamide in refluxing toluene provides dimethoxy compound (**15**). (**13**) is directly transformed into (**15**) by treatment with methanol and rhodium(II) trifluoroacetamide in refluxing toluene (eq 11).[17]



(11)

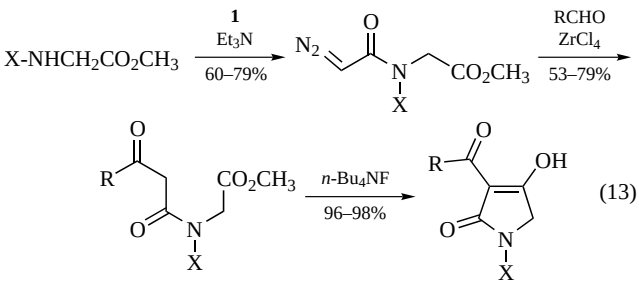
Dimerization Reaction. Dimerization is another commonly encountered reaction of diazo compounds. Alcohol (**16**) is initially transformed into diazoester (**17**) with compound (**1**) and then converted to bisdiazocarbonyl compound (**18**). The intramolecular coupling of this mixed diazo compound with a catalytic amount of $Rh_2(OAc)_4$ produces a 1:1 mixture of (**19**) and (**20**). Furthermore, treatment of (**19**) with a catalytic amount of iodine quantitatively converts (**19**) to (**20**) (eq 12).[18]



(12)

Reaction with Aldehyde. Reaction of aldehydes (*prim*-, *sec*-, and *tert*-) with the diazoacetamide of *N*-substituted glycinate, prepared from the amino ester and (**1**), affords β-keto amides in good to high yields in the presence of Zr(IV) chloride in CH_2Cl_2. Further treatment with *n*-Bu_4NF in THF leads to *N*-protected 3-acyltetramic acids (eq 13).[19]

Cholesteryl diazoacetate (**21**) is readily prepared by the treatment of cholesterol with compound (**1**). Reaction of aldehyde (**22**) with the diazoacetate (**21**) in the presence of a catalytic amount of $SnCl_2$ afforded β-oxo ester (**23**) in good yield (eq 14).[20]



(13)

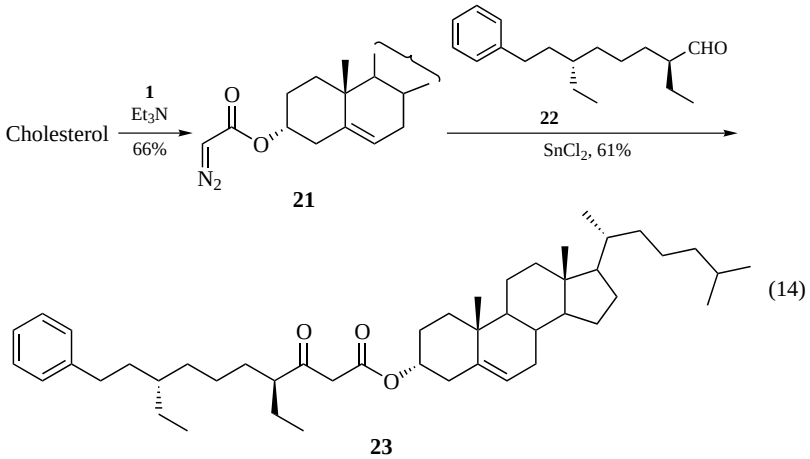
Other Reactions. Shi and co-workers have reported an unusual reaction of β-hydroxy α-diazo carbonyl compounds with compound (**1**). When the reaction of β-hydroxy α-diazo carbonyl compounds and compound (**1**) is carried out in the presence of Et_3N, instead of the desired bisdiazo esters, β-(*p*-tolylsulfonyl) α,β-unsaturated carbonyl compounds or β-(*p*-tolylsulfonyl) α-diazo esters are obtained in good to high yields (eq 15).[21]

Intramolecular C–H insertion reaction of the α-diazoacetyl ester derived from compound (**1**) is also reported recently.[22] The cyclization, found to proceed with excellent regio- and stereoselectivities, and has been used as key step to synthesize natural products.

Radioactively labeled α-diazo esters, which are easily prepared from the corresponding alcohols and the reagent (**1**), have been used as photoaffinity labels.[23]

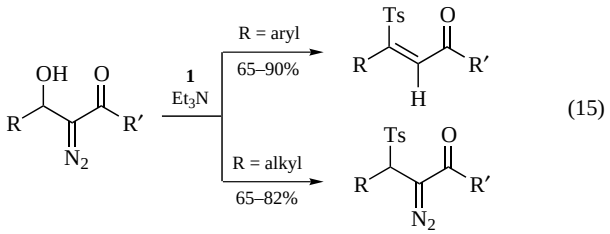
Related Reagents. Compound (**1**) can be converted to reagents that undergo further transformation to a variety of diazo carbonyl compounds. Succinimidyl diazoacetate **(24)** is easily obtained by the reaction of *N*-hydroxysuccinimide with compound (**1**) is a stable, easily stored solid that is highly selective toward diazoacetyl transfer to amines and phenols (eq 16).[24]

The related phthalimidyl diazoacetate **(25)** has yielded series of diazoacetamides bearing Oppolzer's camphorsultam chiral auxiliary (eq 17).[25]



(14)

Diazo acid chloride (**26**) can be prepared from compound (**1**). Chloride (**26**) is an efficient reagent for preparing diazo dicarbonyl compounds from the corresponding alcohols or amines (eq 18).[26]



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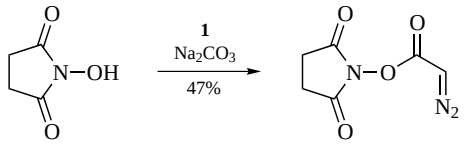

(16)

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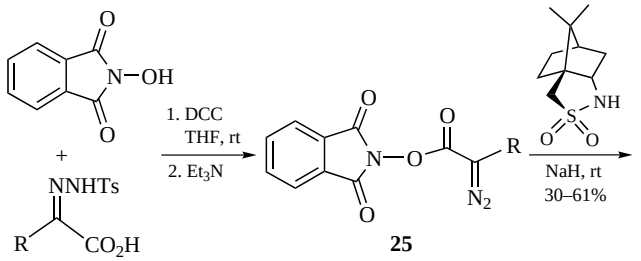

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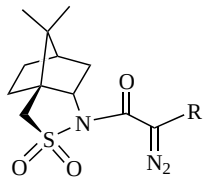

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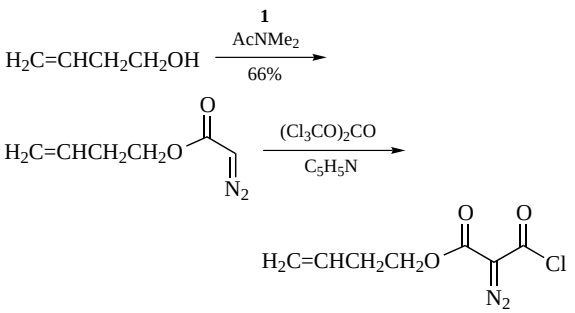

(18)

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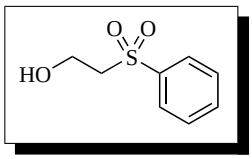
1. (a) House, H. O.; Blankley, C. J., *J. Org. Chem.* **1968**, *33*, 53. (b) Corey, E. J.; Myers, A. G., *Tetrahedron Lett.* **1984**, *25*, 3559. Corey, E. J.; Myers, A. G., *J. Am. Chem. Soc.* **1985**, *107*, 5574. (c) Ramaiah, M.; Nagabhushan, T. L., *Synth. Commun.* **1986**, *16*, 1049. (d) Clive, D. L. J.; Daigneault, S., *J. Chem. Soc., Chem. Commun.* **1989**, 332. Clive, D. L. J.; Daigneault, S., *J. Org. Chem.* **1991**, *56*, 3801. (e) Deshmukh, A. R. A. S.; Bhawal, B. M.; Panse, D. G.; Kulkarni, G. H., *Org. Prep. Proced. Int.* **1989**, *21*, 509. (f) Blankley, C. J.; Sauter, F. J.; House, H. O., *Org. Synth., Coll. Vol.* **1973**, *5*, 258.
2. (a) Martin, S. F.; Austin, R. E.; Oalmann, C. J., *Tetrahedron Lett.* **1990**, 4731. (b) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; DeLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohn, J.; Kleinert, H. D., *J. Med. Chem.* **1992**, *35*, 1710. (c) Martin, S. F.; Oalmann, C. J.; Liras, S., *Tetrahedron Lett.* **1992**, 6727.
3. (a) Womack, E. B.; Nelson, A. B., *Org. Synth., Coll. Vol.* **1955**, *3*, 392. (b) Searle, N. E., *Org. Synth., Coll. Vol.* **1963**, *4*, 424.
4. White, E. H.; Baumgarten, R. J., *J. Org. Chem.* **1964**, *29*, 2070.
5. (a) Regitz, M., *Chem. Ber.* **1965**, *98*, 1210. (b) Regitz, M.; Menz, F.; Ruter, J., *Tetrahedron Lett.* **1967**, 739.
6. Harvey, G., *J. Org. Chem.* **1966**, *31*, 1587,
7. Baumgarten, R. J., *J. Org. Chem.* **1967**, *32*, 484.
8. Cane, D. E.; Thomas, P. J., *J. Am. Chem. Soc.* **1984**, *106*, 5295. Mori, K.; Tsuji, M., *Tetrahedron* **1988**, *44*, 2835.
9. Mak, C. P.; Baumann, K.; Mayerl, F.; Mayerl, C.; Fliri, H., *Heterocycles* **1982**, *19*, 1647.
10. Terasawa, T.; Ikekawa, N.; Marisaki, M., *Chem. Pharm. Bull.* **1986**, *34*, 931. Middlemas, D. S.; Raftery, M. A., *Biochemistry* **1987**, *26*, 1219. Terasawa, T.; Ikekawa, N.; Morisaki, M., *Chem. Pharm. Bull.* **1986**, *34*, 935. Kline, T. B.; Nelson, D. L.; Namboodiri, K., *J. Med. Chem.* **1990**, *33*, 950. Sen, R.; Singh, A. K.; Balogh-Nair, V.; Nakanishi, K., *Tetrahedron* **1984**, *40*, 493. Prestwich, G. D.; Golec, F. A.; Andersen, N. H., *J. Label. Comp. Radiopharm.* **1984**, *21*, 593. Prestwich, G. D.; Singh, A. K.; Carvalho, J. F.; Koeppe, J. K.; Kovalick, G. E., *Tetrahedron* **1984**, *40*, 529. Ujváry, I.; Eng, W.; Prestwich, G. D., *J. Label. Comp. Radiopharm.* **1989**, *28*, 65.
11. Keilbaugh, S. A.; Thornton, E. R., *J. Am. Chem. Soc.* **1983**, *105*, 3283.
12. (a) Ye, T.; McKervey, M. A., *Chem. Rev.* **1994**, *94*, 1091. (b) Doyle, M. P.; McKervey, M. A.; Ye, T., *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-Interscience: New York 1998.
13. (a) Martin, S. F.; Oalmann, C. J.; Liras, S., *Tetrahedron* **1993**, *49*, 3521. (b) Pellicciari, R.; Marinozzi, M.; Natalini, B.; Costantino, G.; Luneia, R.; Giorgi, G.; Moroni, F.; Thomsen, C., *J. Med. Chem.* **1996**, *39*, 2259. (c) Martin, S. F.; Hillier, M. C., *Tetrahedron Lett.* **1998**, *39*, 2929. (d) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S., *J. Org. Chem.* **2000**, *65*, 1305. (e) Hillier, M. C.; Davidson, J. P.; Martin, S. F., *J. Org. Chem.* **2001**, *66*, 1657. (f) Yu, M.; Lynch, V.; Pagenkopf, B. L., *Org. Lett.* **2001**, *3*, 2563. (g) Pellicciari, R.; Costantino, G.; Marinozzi, M.; Macchiarulo, A.; Amori, L.; Flor, P. J.; Gasparini, F.; Kuhn, R.; Urwyler, S., *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3179. (h) Reichelt, A.; Gaul, C.; Frey, R. R.; Kennedy, A.; Martin, S. F., *J. Org. Chem.* **2002**, *67*, 4062. (i) Fillion, E.; Beingessner, R. L., *J. Org. Chem.* **2003**, *68*, 9485. (j) Cheng, Q. F.; Xu, X. Y.; Ma, W. X.; You, T. P., *Chin. Chem. Lett.* **2005**, *16*, 331.
14. (a) Isaacs, L.; Diederich, F., *Helv. Chim. Acta* **1993**, *76*, 2454. (b) Haddad, N.; Galili, N., *Tetrahedron: Asymmetry* **1997**, *8*, 3367.
15. Kim, G.; Kang, S.; Kim, S. N., *Tetrahedron Lett.* **1993**, *34*, 7627.
16. Alt, M.; Maas, G., *Chem. Ber.* **1994**, *127*, 1537.
17. Moody, C. J.; Miller, D. J., *Tetrahedron* **1998**, *54*, 2257.
18. Doyle, M. P.; Hu, W.; Phillips, I. M., *Org. Lett.* **2000**, *2*, 1777.
19. Iida, T.; Hori, K.; Nomura, K.; Yoshii, E., *Heterocycles* **1994**, *38*, 1839.
20. Yang, Z.; Attygalle, A. B.; Meinwald, J., *Synthesis* **2000**, 1936.
21. Shi, W.; Zhang, B.; Liu, B.; Xu, F.; Xiao, F.; Zhang, J.; Zhang, S.; Wang, J., *Tetrahedron Lett.* **2004**, *45*, 4563.
22. (a) Wee, A. G. H., *J. Org. Chem.* **2001**, *66*, 8513. (b) Zhou, X.-T.; Carter, R. G., *Chem. Commun.* **2004**, 2138.
23. (a) Lei, H.; Atkinson, J., *J. Org. Chem.* **2000**, *65*, 2560. (b) Nikonov, A. A.; Valiyaveettil, J. T.; Leal, W. S., *Chem. Senses* **2001**, *26*, 49. (c) Lee, H.-K.; Zheng, Y. F.; Xiao, X.-Y.; Bai, M.; Sakakibara, J., Ono, T.; Prestwich, G. D., *Biochem. Biophys. Res. Commun.* **2004**, *315*, 1.
24. (a) Quihia, A.; René, L.; Guilhem, J.; Pascard, C.; Badet, B., *J. Org. Chem.* **1993**, *58*, 1641. (b) Doyle, M. P.; Kalinin, A. V., *J. Org. Chem.* **1996**, *61*, 2179.
25. Ma, M.; Peng, L.; Li, C.; Zhang, X.; Wang, J., *J. Am. Chem. Soc.* **2005**, *127*, 15016.
26. Moody, C. J.; Slawin, A. M. Z.; Willows, D., *Org. Biomol. Chem.* **2003**, *1*, 2716.

H

2-Hydroxyethyl Phenyl Sulfone



[20611-21-6] $C_8H_{10}O_3S$ (MW 186.2)

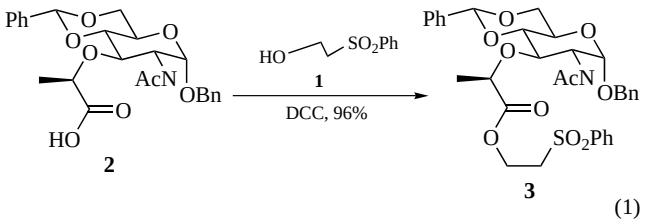
InChI = 1/C8H10O3S/c9-6-7-12(10,11)8-4-2-1-3-5-8/h1-5,9H, 6-7H2

InChIKey = PQVYYVANSPZIKE-UHFFFAOYAD

(protection of carboxylic acids;[1] preparation of a chloroformate reagent for protecting alcohols and amines;[2] protection of phosphates and phosphonates;[3] preparation of a phosphitylation reagent for nucleotide synthesis;[4] 2-ethanol carbanion equivalent;[5] preparation of a triflate reagent for amine quaternization[6])

Alternate Name: 2-(phenylsulfonyl)ethanol.
Physical Data: bp 177 °C/2 mmHg.
Solubility: soluble in organic solvents.
Form Supplied in: colorless liquid.
Analysis of Reagent Purity: NMR, HPLC.
Purity: distillation.
Handling, Storage, and Precautions: irritant, handle with gloves in a fume hood.

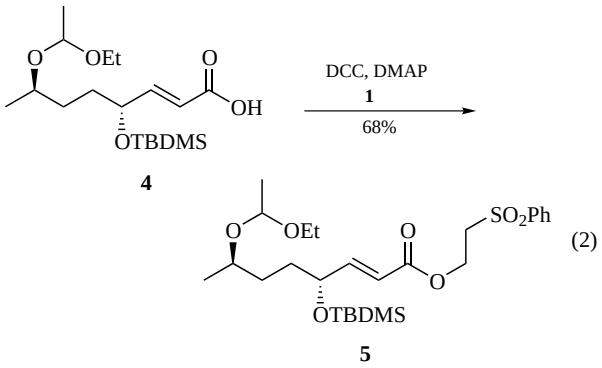
Protection of Carboxylic Acids. 2-Hydroxyethyl phenyl sulfone (**1**) is a useful reagent for the protection of carboxylic acids.[1] Thus, treatment of the protected muramic acid derivative (**2**) with (**1**) and DCC afforded the 2-(phenylsulfonyl)ethyl ester (**3**) in excellent yield (eq 1).[1a]



(1)

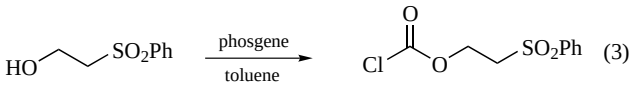
In another example, the unsaturated acid **4** was protected in the same manner to afford ester **5** (eq 2).[1b,c]

The 2-(phenylsulfonyl)ethyl ester is stable to acidic conditions [tetrahydropyranyl (THP), *tert*-butoxycarbonyl (BOC), and ethoxyethyl (EE) groups can be selectively removed], and to oxidation (peroxide) but can be readily removed by treatment with DBU. Note that in both examples cited above, the 2-(phenylsulfonyl)ethyl ester was cleaved without causing epimerization of the acid. The closely related reagent, 2-(*p*-toluenesulfonyl)ethanol, has also been used as a carboxylic acid protecting group.[1d,e] The two reagents work equally well for this purpose and both are commercially available.



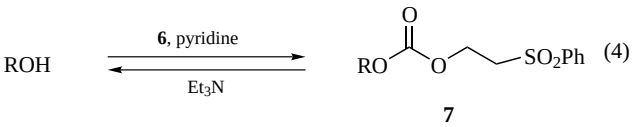
(2)

Preparation of a Chloroformate Reagent (6) for the Protection of Alcohols and Amines. Reaction of (**1**) with phosgene affords the chloroformate (**6**) (eq 3),[2a] a useful reagent for the protection of alcohols[2a,b] and amines.[2c,d]



(3)

Chloroformate (**6**) reacts with alcohols in pyridine at room temperature to afford carbonates (**7**).[2a] The 2-phenylsulfonylethoxycarbonyl (PSEC) group is stable to the conditions required to cleave tetrahydropyranyl (THP) ethers, 2-trimethylsilylethoxy carbonates (TEOC), and levulinate and benzoate esters.[2a,b] The alcohol can be regenerated when desired by treatment with triethylamine in pyridine (eq 4).

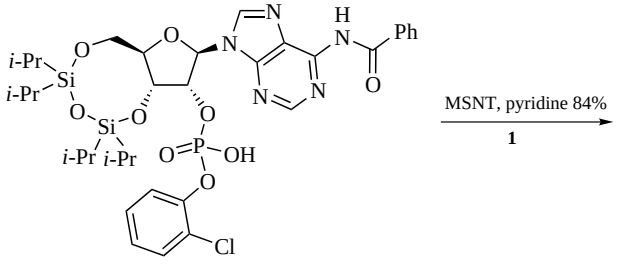


(4)

Reagent (**6**) has also been used to protect amines, generating carbamates which are readily cleaved under mild basic conditions.[2c,d] In one case, the carbamate resulting from reaction of (**6**) with daunomycin was proposed as a potential prodrug for daunomycin.[2d] As mentioned above for carboxylic acid protection, similar chemistry has been reported using 2-(*p*-toluenesulfonyl)ethanol instead of (**1**).

Protection of Phosphates and Phosphonates. 2-Hydroxyethyl phenyl sulfone (**1**) has been used to differentially protect phosphate esters for nucleotide synthesis.[3a,b] Thus, reaction of the diphosphate (**8**) with **1** and 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) in pyridine afforded the differentially protected phosphate **9** in very good yield (eq 5).[3a] The 2-phenylsulfonylethyl phosphate can be cleaved under mild conditions by treatment with triethylamine.

Alcohol (**1**) has also been used to protect a phosphonic acid (**10**) as part of a synthesis of cyclic nucleotides (eq 6).[3c]



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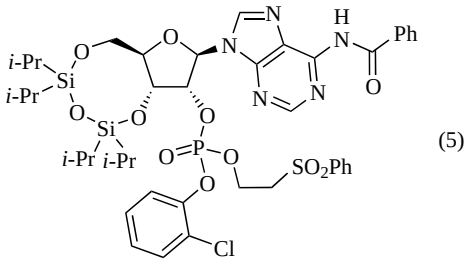

(5)

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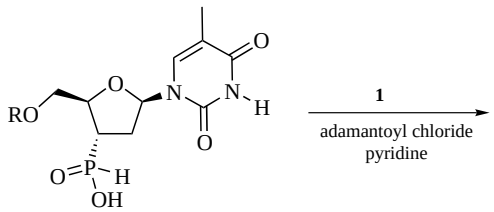
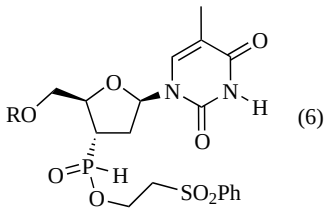


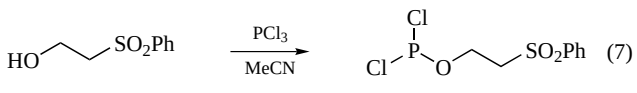
10, R = dimethoxytrityl



(6)

11

Preparation of a Phosphitylation Reagent (12) for Nucleotide Synthesis. The phosphitylation reagent (**12**), useful for nucleotide synthesis, is readily prepared by reaction of (**1**) with phosphorus trichloride in acetonitrile (eq 7).[4a,b]

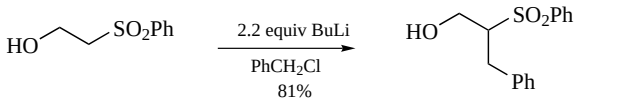


(7)

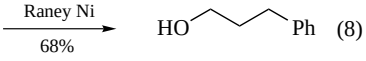
1 **12**

Reagent (**12**) is an easily handled solid which is stable for at least one year when stored in a freezer.[4b]

Use as a 2-Ethanol Carbanion Equivalent. Treatment of (**1**) with more than 2 equiv of butyllithium followed by treatment of the resulting dianion with 1 equiv of an electrophile and removal (either reductively or by elimination) of the phenylsulfonyl group results in a net addition of a 2-ethanol carbanion to the electrophile.[5] Thus, reaction of (**1**) with 2.2 equiv of butyllithium followed by quenching of the dianion with benzyl chloride afforded intermediate (**13**) in very good yield (eq 8).[5a] Desulfurization of (**13**) with Raney nickel afforded 3-phenylpropanol (**14**) in good yield.



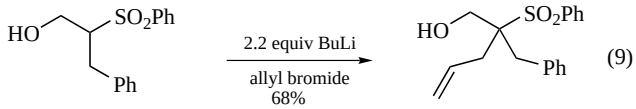
1 **13**



(8)

14

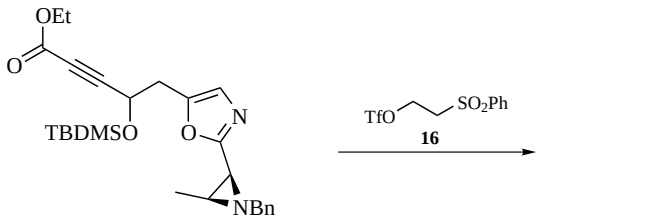
The initial alkylation product can be subjected to a second alkylation to afford a more highly substituted product. For example, alkylation of (**13**) with allyl bromide provides the di-substituted analog (**15**) (eq 9).[5c] These bis-alkylated products have been elaborated further to furanones[5b] and furans.[5c]



(9)

13 **15**

Preparation of a Triflate Reagent (16) for Nitrogen Quaternization. Reaction of **1** with triflic anhydride in pyridine affords the triflate (**16**) in excellent yield (86%).[6] Triflate (**16**) reacted with oxazole (**17**) to afford the quaternized oxazole (**18**) (eq 10). Subsequently, (**18**) was reduced with sodium borohydride to afford a dihydro-oxazole with a phenylsulfonylethyl substituent on the tertiary nitrogen. Thus, (**16**) was used to activate the oxazole ring to chemistry which generated a protected secondary amine.



17

(10)

18

1. (a) Hitchcock, S. A.; Eid, C. N.; Aikins, J. A.; Zia-Ebrahimi, M.; Blaszczak, L. C., *J. Am. Chem. Soc.* **1998**, *120*, 1916. (b) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B., *Tetrahedron Lett.* **1991**, *32*, 1495. (c) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B., *Tetrahedron Lett.* **1991**, *32*, 1499. (d) Roush, W. R.; Blizzard, T. A., *J. Org. Chem.* **1984**, *49*, 4332. (e) Colvin, E. W.; Purcell, T. A.; Raphael, R. A., *J. Chem. Soc. Chem. Comm.* **1972**, 1031.

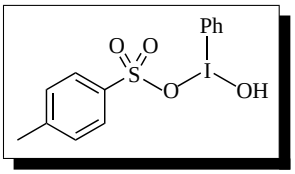
2. (a) Balgobin, N.; Josehpson, S.; Chattopadhyaya, J. B., *Tetrahedron Lett.* **1981**, *22*, 3667. (b) Josephson, S.; Balgobin, N.; Chattopadhyaya,

J., *Tetrahedron Lett.* **1981**, *22*, 4537. (c) Nyilas, A.; Foldesi, A.; Chattopadhyaya, J., *Nucleosides Nucleotides* **1988**, *7*, 787. (d) Maligres, P. E.; Nicolaou, K. C.; Wrasidlo, W., *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1051.

3. (a) Zhou, X.; Remaud, G.; Chattopadhyaya, J., *Tetrahedron* **1988**, *44*, 6471. (b) Sund, C.; Foldesi, A.; Yamakage, S.; Agback, P.; Chattopadhyaya, J., *Tetrahedron* **1991**, *47*, 6305. (c) Zeng, F.; Jones, R. A., *Nucleosides Nucleotides* **1996**, *15*, 1679.
4. (a) Balgobin, N.; Chattopadhyaya, J., *Acta. Chem. Scand. Ser. B.* **1985**, *39*, 883. (b) Claesen, C. A. A.; Segers, R. P. A. M.; Tesser, G. I., *Rec. Trav. Chim. Pays. Bas.* **1985**, *104*, 119.
5. (a) Julia, M.; Uguen, D.; Callipolitis, A., *Bull. Soc. Chim. Fr.* **1976**, 519. (b) Tanaka, K.; Ootake, K.; Imai, K.; Tanaka, N.; Aritsune, K. *Chem. Lett.* **1983**, 633. (c) Jung, J. H.; Lee, J. W.; Oh, D. Y., *Tetrahedron Lett.* **1995**, *36*, 923.
6. Vedejs, E.; Piotrowski, D. W.; Tucci, F. C., *J. Org. Chem.* **2000**, *65*, 5498.

T. A. Blizzard
Merck Research Laboratories, Rahway, NJ, USA

[Hydroxy(tosyloxy)iodo]benzene



[27126-76-7] $C_{13}H_{13}IO_4S$ (MW 392.22)
InChI = 1/C13H13IO4S/c1-11-7-9-13(10-8-11)19(16,17)18-14(15)12-5-3-2-4-6-12/h2-10,15H,1H3
InChIKey = LRIUKPUCKCECPT-UHFFFAOYAS

(reagent for the phenyliodination and oxytosylation of various functional groups;[4] excellent Hofmann reagent;[16] useful for bis-lactonizations,[7] oxidations and oxidative transformations[20])

Alternate Names: HTIB; Koser's reagent; phenyliodine(III) (hydroxyl)tosylate.

Physical Data: nearly colorless crystalline solid (pale 'yellow' cast); mp 140–142 °C,[2] 136–138.5 °C.[3]

Solubility: insoluble in Et_2O; largely insoluble in CH_2Cl_2, $CHCl_3$, MeCN (rt); moderately soluble in H_2O; soluble in MeCN (reflux), MeOH, DMSO.

Form Supplied in: white solid; commercially available in 96% purity.

Preparative Methods: conveniently prepared by the treatment of (diacetoxyiodo)benzene/MeCN mixtures with warm solutions of *p*-toluenesulfonic acid in MeCN. When the acid is introduced, $PhI(OAc)_2$ 'dissolves' to give deep yellow solutions from which HTIB readily separates. If the reaction mixtures are kept near the reflux temperature, the crystallization of HTIB from the solvent can be controlled. At lower temperatures, HTIB separates more rapidly but can, if necessary, be recrystallized by heating the final mixtures of dissolution or from fresh MeCN. Preparations of HTIB can be readily conducted on a 50–100 g scale.

Handling, Storage, and Precautions: a fairly stable compound which may be stored at rt; for extended storage, keep refrigerated in a dark bottle.

Original Commentary

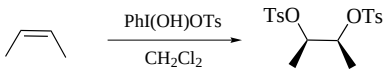
Gerald F. Koser
University of Akron, Akron, OH, USA

General Considerations. Although hydroxy(tosyloxy)iodobenzene is largely insoluble in CH_2Cl_2, $CHCl_3$, and MeCN at rt, all are excellent solvents for the mediation of HTIB reactions. When HTIB is employed in CH_2Cl_2, the completion of a reaction is signaled by the disappearance of the crystalline phase as the iodane is consumed. Since HTIB/MeCN mixtures afford deep yellow solutions at the reflux temperature, reactions conducted under these conditions can sometimes be followed by the fading of the color. HTIB is soluble in MeOH and in this solvent may lead to products containing one or more methoxy groups. DMSO should probably be avoided since HTIB may be reduced by this solvent under some conditions. Acetone reacts with HTIB.

HTIB is mildly electrophilic at iodine and may conveniently be regarded as the chemical equivalent of hydroxy(phenyl)iodonium tosylate[$PhI^{+}OH\ ^{-}OTs$]. Thus HTIB reacts with a variety of organic substrates to give either phenyliodonium tosylates or tosylate esters. Phenyliodination occurs first and whether such reactions proceed to the oxytosylation stage depends on the stability of the iodonium compounds toward nucleophilic collapse. HTIB is also a mild oxidizing agent.

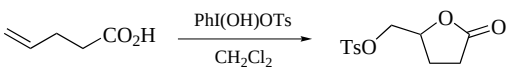
Selected Transformations of Organic Functional Groups.

Alkenes, Dienes. The treatment of alkenes with HTIB (CH_2Cl_2) affords *vic*-ditosyloxyalkanes.[4] Dioxytosylation is thought to be initiated by the *trans* addition of HTIB to the carbon–carbon double bond, and, with alkyl-substituted alkenes, ultimately proceeds with *cis* stereospecificity (eq 1). In some cases (i.e. norbornene, neat styrene), dioxytosylation is accompanied by skeletal rearrangements. Several dienes have been observed to undergo conjugate dioxytosylation with HTIB but the 1,4-ditosyloxyalkenes are not very stable, and the yields are low.[4,5]



(1)

Alkenoic and Alkenedioic Acids. Participation of the carboxyl group occurs when unconjugated alkenoic acids are mixed with HTIB.[6] Of seven alkenoic acids studied, five gave tosyloxylactones (eq 2). In two cases, 'TsOH' was eliminated, and unsaturated lactones[6] were obtained, elimination apparently being favored by alkyl substitution at the carbon–carbon double bond. The oxytosyllactonization of 5-norbornene-*endo*-2-carboxylic acid proceeds with skeletal rearrangement. Alkenic dicarboxylic acids react with HTIB (CH_2Cl_2, rt) to give bis-lactones (eq 3).[7] More significantly, bis-lacton ization proceeds with *cis* stereospecificity. The mildness and operational convenience of the HTIB procedure recommend this approach as an excellent alternative to methods requiring the treatment of alkenedioic acids or their tetrabutylammonium salts with an excess of lead(IV) acetate[8] or the treatment of silver alkenedioates with iodine/silver(I) acetate.[9]



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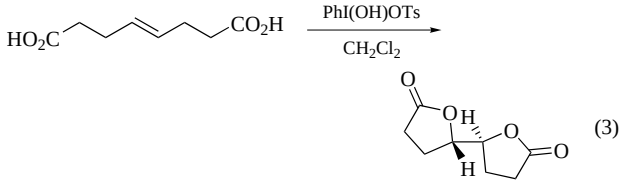
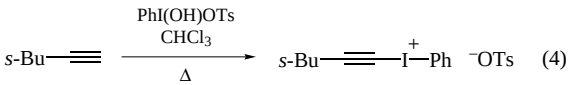


(3)

Alkynes. Terminal alkynes react with HTIB in $CHCl_3$ under reflux to give either alkynyl(phenyl)iodonium tosylates, β-tosyloxyvinyl(phenyl) iodonium tosylates, or mixtures of both.[10] The production of alkynyliodonium salts is favored by the presence of either aryl or bulky alkyl (e.g. *t*-Bu, *s*-Bu) groups in the alkyne (eq 4), while terminal alkynes with linear alkyl groups lead exclusively to the vinyliodonium compounds (eq 5). A desiccant (silica bead) has been employed with HTIB in CH_2Cl_2 (rt) to facilitate the alkynyliodonium pathway with propyne and 1-hexyne, but the product yields were low.[11] Internal alkynes afford β-tosyloxyvinyliodonium tosylates with HTIB.[10] When HTIB is employed in methanol, both terminal and internal alkynes undergo oxidative rearrangement to give carboxylate esters, $R^1R^2CHCO_2Me$.[12]



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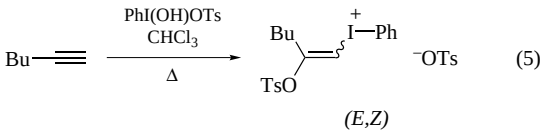
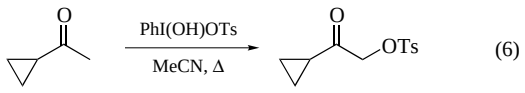


(5)

(E,Z)

Ketones, β-Dicarbonyl Compounds, Silyl Enol Ethers, Silyl Ketene Acetals. The treatment of ketones with HTIB (MeCN or CH_2Cl_2) affords α-toxyloxy ketones (eq 6),[13] presumably via α-phenyliodonio ketone tosylates [$RCOC(\overset{+}{I}Ph,{}^{-}OTs$]. Silyl enol ethers ($CH_2Cl_2$, rt) also afford α-tosyloxy ketones with HTIB and can be employed to direct the regiochemistry of oxytosylation, while esters can be functionalized at α-carbon via their silyl ketene acetals (eq 7).[14] The conversion of β-dicarbonyl compounds to their α-toxyloxy derivatives with HTIB has also been demonstrated.[13] The reactions of 5-oxo- and 4,6-dioxocarboxylic acids with HTIB (CH_2Cl_2) eventuate in the production of keto and diketo lactones (eq 8).[15]



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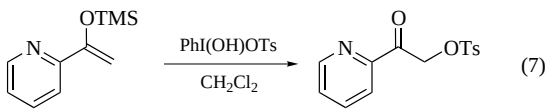

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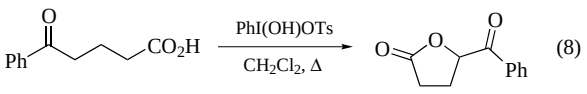
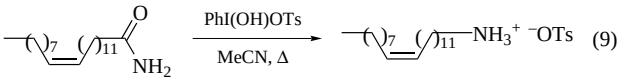


(8)

Carboxamides. One of the most useful applications of HTIB is for the conversion of aliphatic primary carboxamides to amines (MeCN, reflux); the amines separate from the solvent (on cooling) as their hydrogen tosylate salts (eq 9).[16] This is a particularly advantageous method for the production of amines from long-chain amides,[17] which afford low yields (or none) of amines under the standard conditions (e.g. $NaOH/Br_2$, Δ) for the Hofmann reaction. The synthesis of bridgehead amines from carboxamides in the adamantane, cubane, and homocubane series of compounds has also been described.[18] Such reactions proceed via intermediate *N*-phenyliodoniocarboxamide tosylates [$RCONH\overset{+}{I}Ph^{-}OTs$] and their rearrangement with loss of TsOH and iodobenzene to alkyl isocyanates.[19] This is not a good method for the preparation of aromatic amines since they can be oxidized by HTIB as they are produced.



(9)

Further Applications of HTIB. The synthetic utility of HTIB is further underlined by its use for the oxidation of allenes and allenyl ethers (CH_2Cl_2) to aldehydes or ketones,[20] the ligand-transfer oxidation of iodoarenes to give [hydroxy(tosyloxy)iodo] arenes (CH_2Cl_2),[21] the oxidative deiodination of alkyl iodides to alkyl tosylates ($CHCl_3$ or CH_2Cl_2),[22] including cubyl and homocubyl examples,[23] and as an iodination 'catalyst' for the conversion of alkynols to α- and/or β-iodoenones.[24] Various [hydroxy(toxyloxy)iodo]arenes, ArI(OH)OTs, have been employed for the synthesis of diaryliodonium, aryl(2-furyl)iodonium, and aryl(2-thienyl)iodonium tosylates.[25] HTIB has also been used for the conversions of flavanones to flavones (MeOH)[26] and isoflavones (MeCN),[27] aromatic ketones to methyl arylalkanoates (MeOH or $(MeO)_3CH$),[28] chalcones to deoxybenzoins containing the $(MeO)_2CH$ group at the α-carbon (MeOH),[29] and flavonols to their *vic*-dimethoxy adducts (MeOH).[30]

Analogs of HTIB. Various derivatives of HTIB with substituents in the iodoarene nucleus, ArI(OH)OTs,[21,25,31,32] and three arenesulfonyloxy analogs[33] have been reported. [Hydroxy (mesyloxy)iodo]benzene, $PhI(OH)O_3SMe$,[11,14,23,34,35] and [hydroxy((+)-10-camphorsulfonyloxy)iodo]benzene[36] are also known. [Hydroxy((bis(phenyloxy)phosphoryl)oxy)iodobenzene], $PhI(OH)OP(O)(OPh)_2$, shows considerable potential for phosphate ester synthesis. Thus far, the α-oxyphosphorylation of ketones and β-dicarbonyl compounds,[37] the oxyphosphoryllactonization of alkenoic acids,[37] and the conversion of terminal alkynes[38] to monoketol phosphates with HPIB have been reported.

First Update

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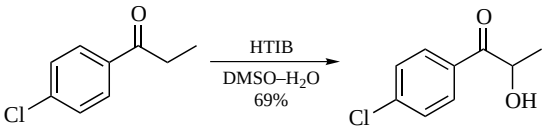
***α*-Hydroxylation and α-Oxytosylation.** Enolizable ketones are directly oxidized to the corresponding α-hydroxy ketones with HTIB in dimethylsulfoxide–water (eq 10).[39] The corresponding

α-hydroxy derivatives are obtained under neutral conditions and in good yields without the formation of α-tosyloxy ketones. The latter are not believed to be involved as intermediates. The amount of water in DMSO [5–15% (v/v)] does not significantly alter the final yields. The reaction is applicable to aromatic or heteroaromatic ketones, and is successful with various substituents on the aromatic ring. However, aliphatic ketones, such as cyclohexanone or 3-pentanone, do not lead to the corresponding α-hydroxyketones under similar reaction conditions. Substituted pyridines are subjected to direct oxidation at the methylene moiety (eq 11).[40] Simple alkylpyridines or 3-substituted derivatives are inert towards this reagent, but 2- and 4-substituted derivatives $PyrCH_2X$ ($X = CO_2R$, COC_6H_5) are oxidized at the CH_2 position. The transformation is effective for compounds in which the reactive center is activated by a strong electron-withdrawing group. The reaction leads to modest yields of the corresponding α-tosyloxy derivatives. Oxytosylation occurs at the α-carbon atom of the imino group of an *N*-acetylardeemin analog, followed by formation of an intermediate tosylate iminium, and subsequent intramolecular Diels–Alder reaction (eq 12).[41–43] Aliphatic carboxylic anhydrides undergo oxytosylation at the α-carbon when an excess of the anhydride is heated with HTIB (eq 13).[44] Treatment of the reaction mixture with MeOH and TsOH affords an α-tosyloxy ester. One-pot reactions of ketones, HTIB, and sodium sulfinates or potassium *O*,*O*-dialkyl selenophosphates lead to the formation of the corresponding β-keto sulfones or Se-(β-oxoalkyl) *O*,*O*-dialkyl selenophosphates, respectively.[45,46]



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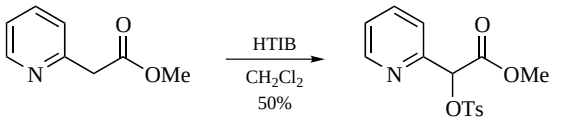

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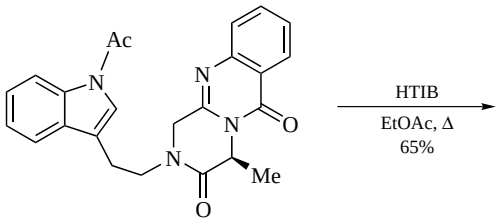
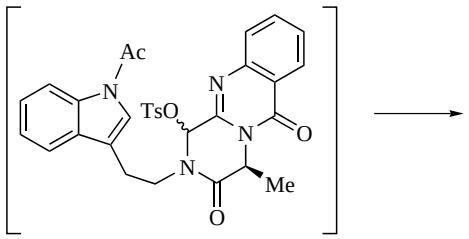
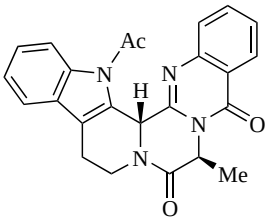
Phenyliodination. Diaryliodonium salts can be prepared by the reaction of arylstannanes and aryl- and vinylboron derivatives with HTIB. The reaction of HTIB with sodium or potassium tetraarylborates in acetic acid involves boron–iodine(III) exchange as well as ligand exchange reactions at room temperature (eq 14).[47] This transformation provides a direct, regioselective route to diaryliodonium tetraarylborates. HTIB reacts with an isopropyl vinyl boronate in the presence of $BF_3{\cdot}OEt_2$ at 0 °C in dichloromethane yielding an iodonium salt in 87% yield (eq 15).[48] The reaction is stereoselective with retention of olefin geometry. Substituted aryltributylstannanes react with HTIB to afford diaryliodonium tosylates (eq 16).[49] In this process, the latter, bearing one or more substituents on one aryl ring, are obtained in modest yields under mild conditions. This procedure has potential utility for making phenyl iodonium salts except for those bearing electron-withdrawing substituents. An alternative procedure allows the preparation of a variety of iodonium derivatives using aryl or heteroaryl boronic acids instead of stannanes (eq 17).[50] This method provides the tosylates with better yields and without the concern of using tin reagents.



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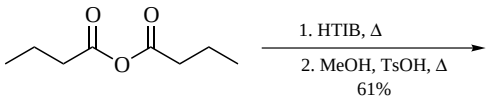

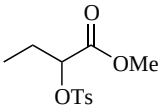
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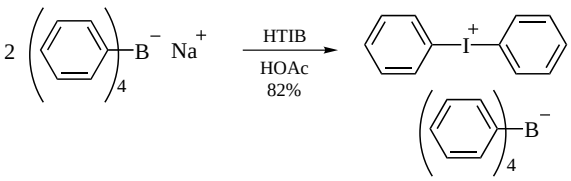

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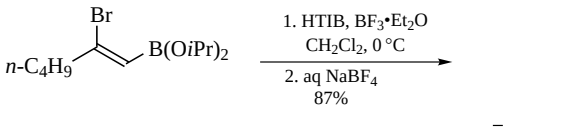

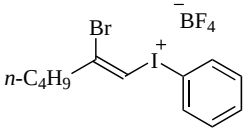
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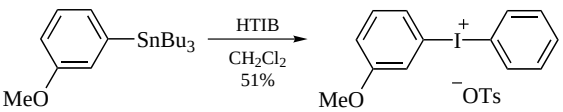

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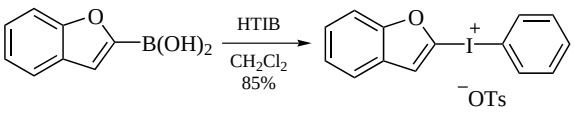
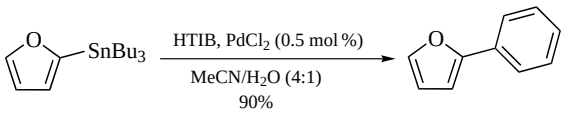


(17)

Palladium-catalyzed Cross-coupling. Although arylstannanes and arylboron derivatives undergo phenyliodination with HTIB and afford aryl(phenyl)iodonium salts, the presence of palladium catalysts in such mixtures results in Stille- and Suzuki-type cross-coupling reactions. The palladium-catalyzed coupling of organostannanes with HTIB at room temperature in aqueous conditions leads to the phenyl-substituted products (eq 18).[51] The reaction proceeds under mild conditions to afford the desired products in very good yields. HTIB undergoes cross-coupling with boronic acids, as well as with boronates and trialkylboranes, to afford biphenyls and aryl-substituted alkenes (eqs 19 and 20).[52] Coupling of phenylboronic acid with HTIB occurs in the presence of $Pd(PPh_3)_4$, with or without base. HTIB is also efficient for coupling with vinylcatecholboronates. Trialkylboranes are used in cross-coupling to afford *trans*-stilbenes (eq 20). Potassium aryltrifluoroborates as organoboron substrates react smoothly with HTIB in the presence of a palladium catalyst under mild conditions to afford biaryls in excellent yields (eq 21).[53] The addition of a base is not required for the reaction of HTIB with potassium aryltrifluoroborates. *N*-Acylbenzotriazoles are obtained directly by the palladium-catalyzed carbonylation of benzotriazoles with HTIB in the presence of carbon monoxide (eq 22).[54]



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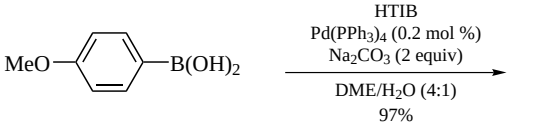

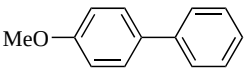

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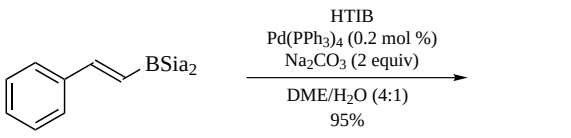

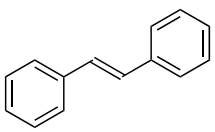

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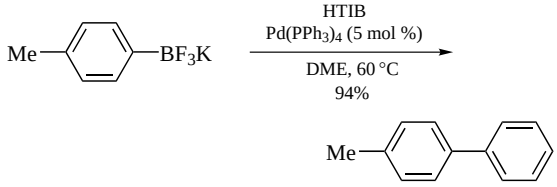

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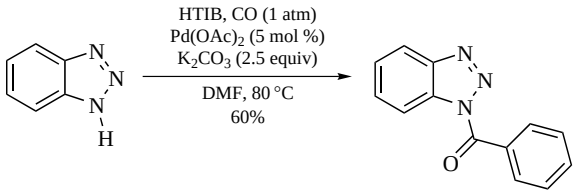
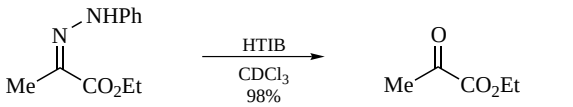


(22)

Oxidative Deprotection. The carbonyl group of α-keto esters can be regenerated from their phenylhydrazones using HTIB under mild conditions (eq 23).[55,56] Both (*E*)- and (*Z*)-phenylhydrazones undergo smooth oxidative hydrolysis with HTIB in high yields. Similarly, the conversion of hydroximates into lactones is achieved using HTIB (eq 24).[57] The sulfide is oxidized to the sulfoxide in the same process (1:1 diastereoisomeric mixture). *N*,*N*-Dialkylhydrazides are efficiently cleaved upon treatment with HTIB to give carboxylic acids in an aqueous/organic medium (eq 25).[58]



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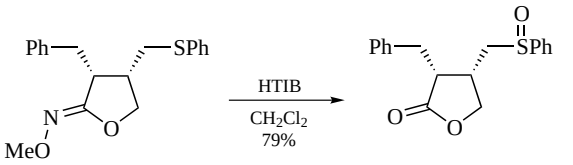

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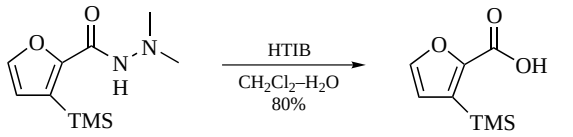
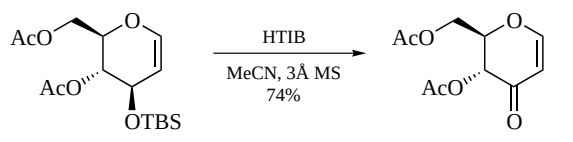


(25)

Acetyl and benzyl protected allylic alcohols of glycals are converted to α,β-unsaturated ketones by a direct oxidation with HTIB.[59–64] The oxidation is independent of the relative stereochemistry as well as the nature of the protecting groups on the pyran ring. A range of protecting groups (e.g., Ac, Bz, Bn, TMS, or TBS) is compatible with the process.[61] 3-*O*-Silyl groups are smoothly converted into a carbonyl giving 2,3-dihydro-4*H*-pyran-4-ones in good yields (eq 26).[62] Unexpectedly, the reaction of 3,4-bis(*O*-TBS)-6-*O*-tosyl-D-glycal with HTIB affords the desired enone only as a minor product. The major products arise via epoxide formation or ring contraction (eq 27).[63] The HTIB oxidation of a perbenzylated glycal leads to the corresponding enone in good yield as well as to ring contraction products (eq 28).[64]



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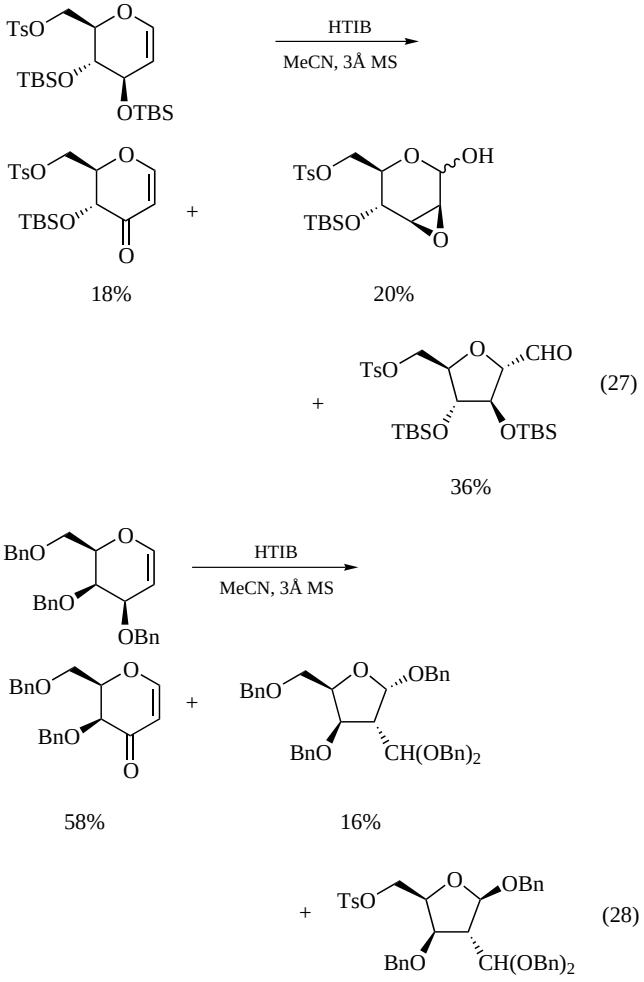
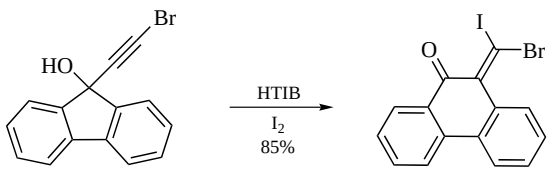
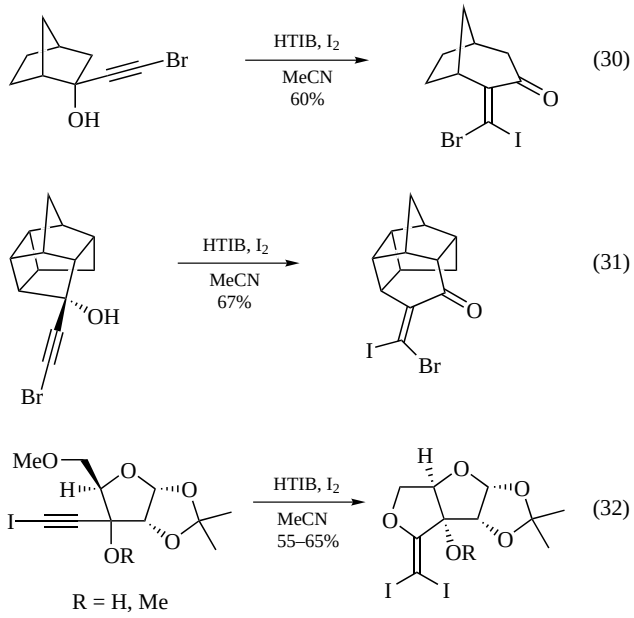
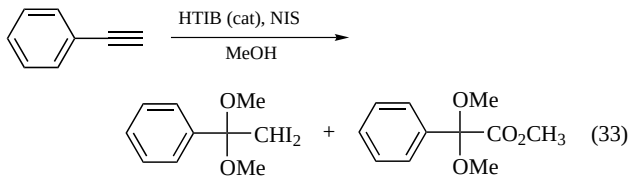


Ring Expansion. HTIB is useful for the preparation of cyclic β,β-dihaloenones from the corresponding bromoethynyl alcohol (eq 29).[65–71] The propargylic alcohol reacts with equimolar amounts of HTIB and iodine under mild conditions to produce cyclohexanone derivatives with a high degree of stereoselectivity. This combination of HTIB and iodine in equimolar quantities can sometimes be replaced by NIS and a catalytic amount of HTIB. The reaction is used in the synthesis of phenanthrenones from the readily available fluorenone derivatives (eq 29).[65] Ring expansion of bicyclic derivatives such as camphor and adamantanone under the same conditions affords (*Z*)-bromoiodoenones in good yield and high stereoselectivity (eq 30).[66,67,70] Interestingly, the analogous ring expansion of a pentacycloundecane derivative affords (*E*)-bromoiodoenone but not the expected (*Z*)-isomer (eq 31).[71] Iodoalkynol derivatives of protected xylofuranose systems (as propargylic alcohols or ethers) react with HTIB and iodine in acetonitrile but do not lead to the same rearrangement (eq 32).[72] β,β-Diiodoenol ethers contained in furan cores are formed via the intramolecular capture of an intermediate iodonium species by the primary methoxy ether.

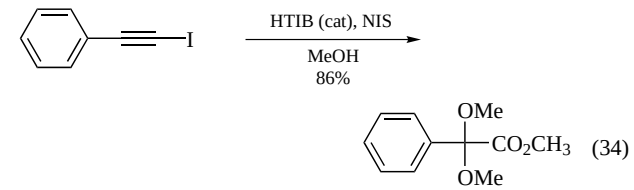


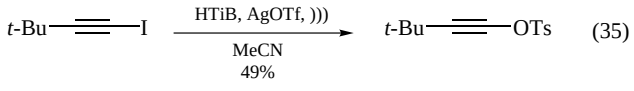


Reaction with Alkynes. Acetals of dihaloacetophenones are prepared from phenylethynes with *N*-halosuccinimide (NIS or NBS) and catalytic amounts of HTIB in methanol (eq 33).[73] When an equimolar quantity of NIS is used in the presence of a catalytic amount of HTIB, α-diiodoacetophenone acetal is formed in an excellent yield. If the ratio of NIS to phenylethyne is increased with concomitant increase in the amount of HTIB, the yield of the acetal decreases to 70% and methyl phenylglyoxylate is formed as a minor product. In this process, there is no evidence of formation of methyl phenylacetate, which is typically formed in the reaction of equimolar HTIB with phenylethyne in hot methanol. The acetal of methyl phenylglyoxylate is also prepared as the sole product by treatment of 2-iodo-1-phenylethyne with NIS and a catalytic amount of HTIB (eq 34).[74] Terminal alkynes are also reported to react with HTIB in an ultrasound enhanced system to furnish arylsulfonates in a quick and simple one-step process (eq 35).[75]

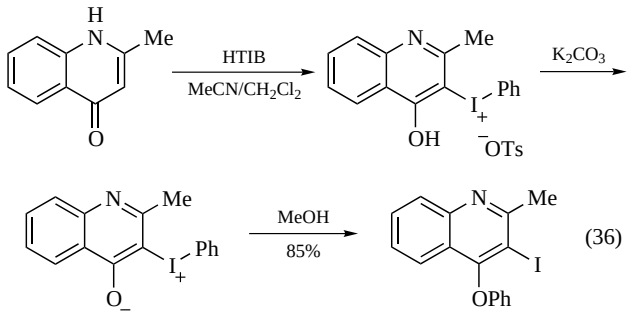


Conditions	Yield (%)	
0.1 equiv HTIB/1.1 equiv NIS	95	-
0.3 equiv HTIB/3.3 equiv NIS	70	30





Iodonium Ylides. Quinolones are readily oxidized to the corresponding quinolines.[76] The oxidation of 2-methyl-4-quinolones with HTIB affords 2-methyl-3-iodo-4-phenoxyquinolines after subsequent treatment with potassium carbonate (eq 36).[76] The initial oxidation step with HTIB affords an α-phenyliodonio tosylate. This tosylate on treatment with a base leads to the formation of a stable iodonium ylide, which undergoes rearrangement to a quinoline upon reflux in methanol. Iodonium betaines are also prepared from a series of 4-aminocoumarins (eq 37).[77] Treatment of 4-aminocoumarins with HTIB in dichloromethane gives 4-amino-3-phenyliodonium coumarin tosylates, which undergo a rearrangement to 3-iodo-4-phenylaminocoumarins upon reflux in acetonitrile. The latter are then deprotonated with NaOH to afford 1,4-iminoiodanes. Other 1,4-iminoiodanes are similarly prepared and isolated as stable solids from the reaction of 2-amino-1,4-naphthoquinones and 2-amino-1,4-quinones with HTIB.[78–80]



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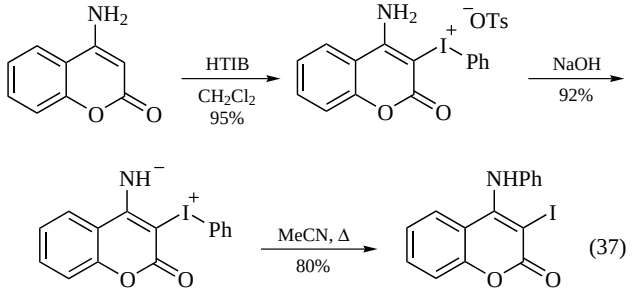
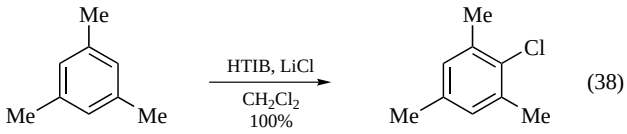


(37)

Halogenation. Polyalkylbenzenes react with HTIB in the presence of inorganic halides or *N*-halosuccinimide to afford ring halogenation products in good yields (eq 38).[81,82] The reaction of mesitylene with HTIB in the presence of lithium chloride gives the monochlorinated product in quantitative yield. The process can be extended to brominations and iodinations with the use of sodium bromide or iodide. In general, such halogenations are highly selective and can be carried out under mild conditions. α-Bromo-β-dicarbonyl systems can also be prepared from treatment of a dione with HTIB and a slight excess of $CuBr_2$ (eq 39).[83] The bromination proceeds via an α-phenyliodonio-β-dione which permits facile displacement of iodobenzene by bromide to give the desired α-bromo-1,3-keto ester in excellent yield.



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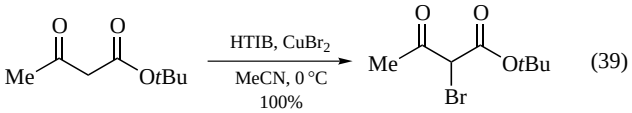
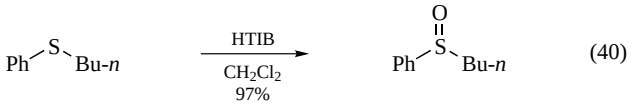


(39)

Sulfur Oxidation. Alkyl- and arylsulfides can be selectively oxidized to the corresponding sulfoxides with HTIB at room temperature (eqs 24 and 40).[57,84,85] This is accomplished with stoichiometric quantities of HTIB in dichloromethane or with iodosylbenzene and 10 mol % TsOH in acetonitrile (i.e., in situ formation of HTIB). In both cases, the oxidation process stops at the stage of a sulfoxide without overoxidation to the sulfone. The oxidation of *p*-tolyl disulfide to the corresponding thiosulfonic ester with 2 equiv of HTIB has also been reported.[86] HTIB can also be used for *O*-glycosylation of thioglycosides (eq 41).[87] This transformation involves the treatment of thioglycosides with HTIB in the presence of alcohols to give high yields of *O*-glycosides albeit with low stereoselectivity. The process occurs via oxidation of the thiophenyl group to a sulfonium intermediate followed by glycosylation.



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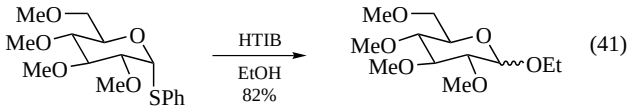
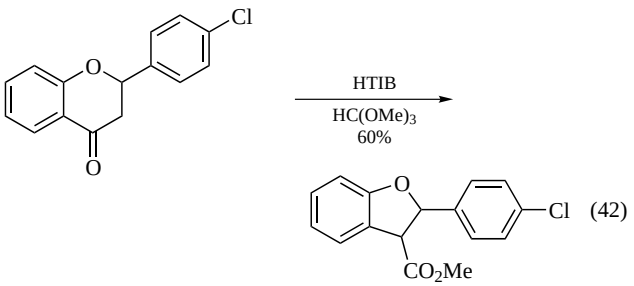


(41)

Other Oxidative Transformations. Flavanones, on oxidation with HTIB in trimethyl orthoformate, undergo a ring contraction by 1,2-aryl shift, yielding methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates as major products (eq 42).[88] The structurally related chromanones undergo dehydrogenation and 2,3-alkyl migration upon reaction with HTIB in acetonitrile (eq 43).[89] Similarly, the spiro derivatives afford the rearranged tetrahydroxanthone products (eq 44).[89] A regiospecific phenyl migration is obtained when a spiro-linked benzofused heterocyclic system is reacted with HTIB under the same conditions.[90] The aromatization of Hantzsch 1,4-dihydropyridines with HTIB is completed within a few minutes in dichloromethane at room temperature (eq 45).[91] 2-Aryl-1,2,3,4-tetrahydro-4-quinolones are oxidized to the corresponding 4-alkoxy-2-arylquinolines upon treatment with HTIB, trimethyl orthoformate, and perchloric acid (eq 46).[92] The initial formation of enol ethers and their phenyliodination at nitrogen is probably responsible for the overall transformation. The transformation of a ketoxime to a nitrosoalkene with HTIB has been reported (eq 47).[93] Oximes of *o*-allyloxyacetophenones afford tricyclic derivatives of 5,6-dihydro-1,2-oxazin-4-one with HTIB in acetonitrile. The reaction proceeds via oxidation of the oxime function to a nitrosoalkene, followed by an intramolecular [4 + 2] cycloaddition and oxidation. Treatment of β-dicarbonyl compounds with HTIB and azidotrimethylsilane affords α-azido-β-dicarbonyl compounds (eq 48).[94,95] Arenecarboxylic acids are transformed into a mixture of lactones and iodinated lactones in the presence of iodine and HTIB albeit in low yields (eq 49).[96] The reaction is thought to occur through a radical mechanism.

Iodinated lactones are produced through the formation of lactone skeletons and iodination of the aromatic rings via an ionic pathway. Phosphoranyl-derived phenyliodonium tosylates are prepared in good yields by the reaction of stabilized phosphonium ylides with HTIB under mild conditions (eq 50).[97,98] The obtained phosphorane-derived phenyliodonium tosylates can react with soft nucleophiles, such as iodide, bromide, benzenesulfinate, and thiophenolate, with selective formation of the corresponding α-functionalized phosphonium ylides, which can be further converted to alkenes by Wittig reaction with benzaldehyde. Finally, the use of HTIB is reported for the construction of a pyrrole derivative via the oxidation of a styryl moiety and cyclization (eq 51).[99]



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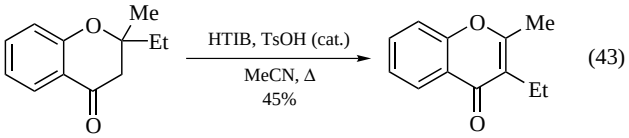

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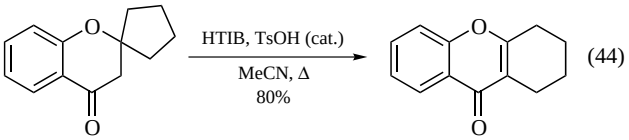

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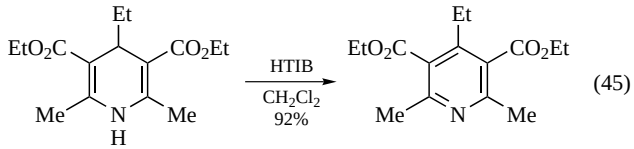

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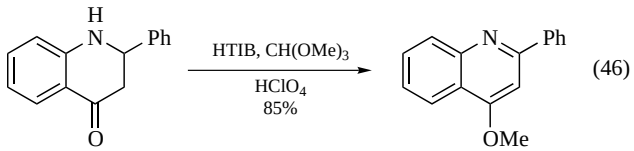

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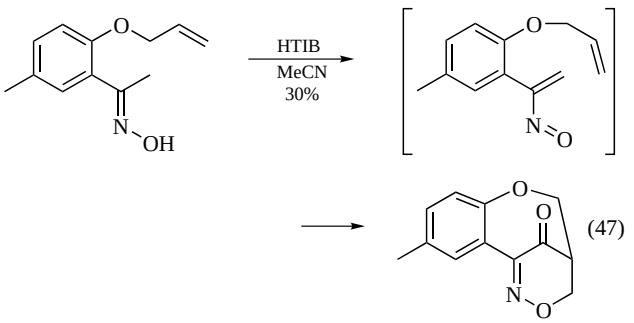

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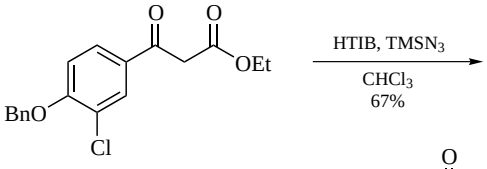

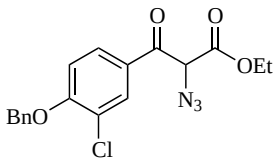

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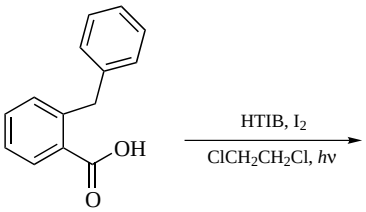

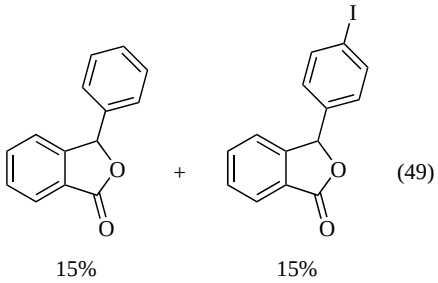

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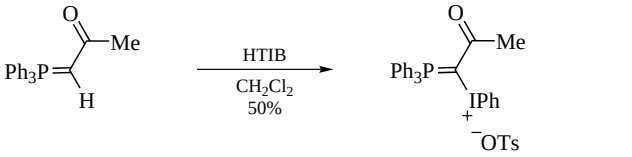

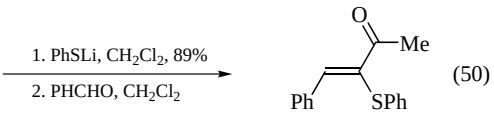

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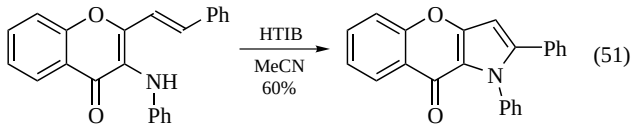
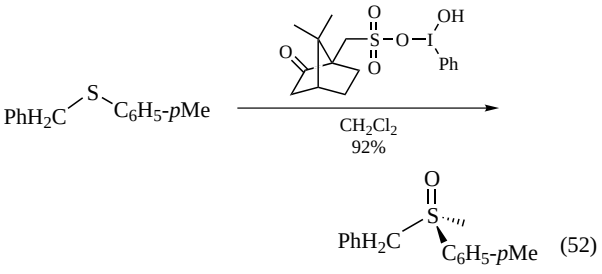


(51)

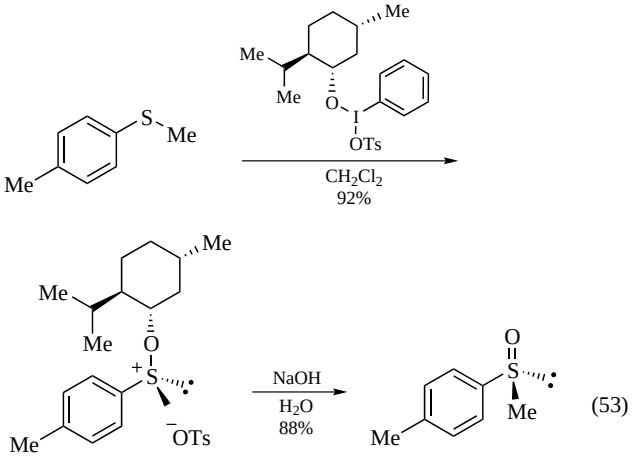
Chiral Analogs of HTIB. The development of chiral analogs of HTIB has only begun recently and is a promising field of research.[100] Such work provides new opportunities for the synthesis of new and more efficient chiral hypervalent iodine reagents for asymmetric synthesis. A series of HTIB analogs possessing the aromatic iodane skeleton has been reported. An asymmetric oxidation of unsymmetrical sulfides to chiral sulfoxides is performed using {hydroxy[(+)-10-(camphorsulfonyl)oxy]iodo}benzene (eq 52).[85]

The sulfoxides are obtained in good yields but low enantioselectivities (3–14% ee). Several HTIB analogs possessing chiral groups are known. {[(+)-Menthyloxy](tosyloxy)iodo} benzene is prepared from [methoxy(tosyloxy)iodo]benzene and equimolar amount of (1*S*,2*R*,5*S*)-(+)-menthol in dichloromethane.[101] This reagent allows the oxidation of unsymmetrical sulfides to [(+)-menthyloxy]sulfonium tosylates transferring the equivalent of a menthyloxenium ion to sulfur with modest diastereoselectivities (4–57% de) (eq 53). Hydrolysis of the sulfonium salts delivers the corresponding sulfoxides. However, separation of the diastereoisomeric (menthyloxy)sulfonium salts by fractional recrystallization and subsequent hydrolysis affords the sulfoxides in moderate to excellent optical purity (49–99% ee). (*R*)-(+)- and (*S*)-(−)-1-Tosyloxy-1,3-dihydro-3-methyl-3-phenylbenziodoxoles are prepared from enantiomerically pure 2-iodo-α-methylbenhydrols by oxidation with HTIB (eq 54).[102] Other analogs possessing chiral *ortho* 1-alkoxyethyl groups are also described.[103–105] Asymmetric oxytosylations of both styrene (eq 55) and propiophenone (eq 56) are reported using these analogs. Enantioselectivities for the dioxytosylation of styrene and for the α-oxytosylation of propiophenone range from 26% to 52% and from 15% to 28%, respectively. 1-Methoxyethyl derivatives give the highest degree of selectivity. A second substituent *ortho* to the iodine atom further increases the selectivity in the additions of these reagents to alkenes. A C_2-symmetrical analog containing (methoxy)propyl groups at both *ortho* positions of the phenyl ring and an analog possessing a (methoxy)propyl or (benzyloxy)propyl group at one *ortho* position are also reported. But the latter do not afford higher selectivities in oxytosylation reactions.



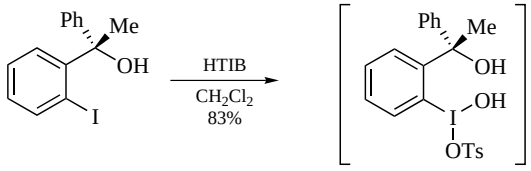
(52)

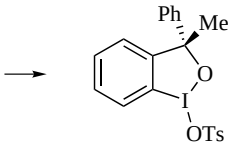
14% ee



(53)

16% de





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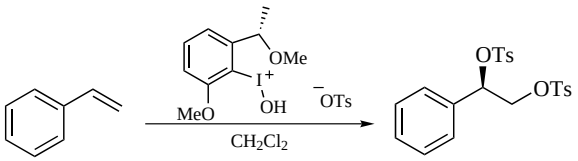

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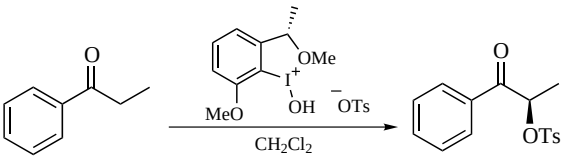


(56)

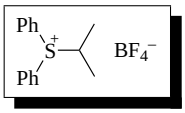
28% ee

1. Moriarty, R. M.; Vaid, R. K.; Koser, G. F., *Synlett* **1990**, 365.
2. Neiland, O.; Karele, B., *J. Org. Chem. USSR (Engl. Transl.)* **1970**, *6*, 889 (first report of HTIB).
3. Koser, G. F.; Wettach, R. H.; Troup, J. M.; Frenz, B. A., *J. Org. Chem.* **1976**, *41*, 3609.
4. Rebrovic, L.; Koser, G. F., *J. Org. Chem.* **1984**, *49*, 2462.
5. Shah, M.; Ph.D. dissertation, The University of Akron, 1988, p 96.
6. Shah, M.; Taschner, M. J.; Koser, G. F.; Rach, N. L., *Tetrahedron Lett.* **1986**, *27*, 4557.
7. Shah, M.; Taschner, M. J.; Koser, G. F.; Rach, N. L. Jenkins, T. E.; Cyr, P.; Powers, D., *Tetrahedron Lett.* **1986**, *27*, 5437.
8. Corey, E. J.; Gross, A. W., *Tetrahedron Lett.* **1980**, *21*, 1819.
9. Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, A., *J. Org. Chem.* **1975**, *40*, 1932.
10. Rebrovic, L.; Koser, G. F., *J. Org. Chem.* **1984**, *49*, 4700.
11. Stang, P. J.; Surber, B. W.; Chen, Z.-C.; Roberts, K. A.; Anderson, A. G., *J. Am. Chem. Soc.* **1987**, *109*, 228.
12. Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Vaid, B. K., *Tetrahedron Lett.* **1987**, *28*, 2845.
13. Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H., *J. Org. Chem.* **1982**, *47*, 2487.
14. Moriarty, R. M.; Penmasta, R.; Awasthi, A. K.; Epa, W. R.; Prakash, I., *J. Org. Chem.* **1989**, *54*, 1101.
15. Moriarty, R. M.; Vaid, R. K.; Hopkins, T. E.; Vaid, B. K.; Prakash, O., *Tetrahedron Lett.* **1990**, *31*, 201.
16. Lazbin, I. M.; Koser, G. F., *J. Org. Chem.* **1986**, *51*, 2669.
17. Vasudevan, A.; Koser, G. F., *J. Org. Chem.* **1988**, *53*, 5158.

18. Moriarty, R. M.; Khosrowshahi, J. S.; Awasthi, A. K.; Penmasta, R., *Synth. Commun.* **1988**, *18*, 1179.
19. Lazbin, I. M.; Koser, G. F., *J. Org. Chem.* **1987**, *52*, 476.
20. Moriarty, R. M.; Hopkins, T. E.; Vaid, R. K.; Vaid, B. K.; Levy, S. G., *Synthesis* **1992**, 847.
21. Koser, G. F.; Wettach, R. H., *J. Org. Chem.* **1980**, *45*, 1542.
22. (a) Zefirov, N. S.; Zhdankin, V. V.; Kozmin, A. S., *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1983**, *32*, 1530. (b) Macdonald, T. L.; Narasimhan, N., *J. Org. Chem.* **1985**, *50*, 5000.
23. Moriarty, R. M.; Khosrowshahi, J. S., *Synth. Commun.* **1989**, *19*, 1395.
24. (a) Angara, G. J.; McNelis, E., *Tetrahedron Lett.* **1991**, *32*, 2099. (b) Angara, G. J.; Bovonsombat, P.; McNelis, E., *Tetrahedron Lett.* **1992**, *33*, 2285. (c) Bovonsombat, P.; McNelis, E., *Tetrahedron Lett.* **1992**, *33*, 7705. (d) Bovonsombat, P.; McNelis, E., *Tetrahedron* **1993**, *49*, 1525.
25. (a) Koser, G. F.; Wettach, R. H.; Smith, C. S., *J. Org. Chem.* **1980**, *45*, 1543. (b) Carman, C. S.; Koser, G. F., *J. Org. Chem.* **1983**, *48*, 2534. (c) Margida, A. J.; Koser, G. F., *J. Org. Chem.* **1984**, *49*, 3643.
26. Prakash, O.; Pahuja, S.; Moriarty, R. M., *Synth. Commun.* **1990**, *20*, 1417.
27. Prakash, O.; Pahuja, S.; Goyal, S.; Sawhney, S. N.; Moriarty, R. M., *Synlett* **1990**, 337.
28. Prakash, O.; Goyal, S.; Moriarty, R. M.; Khosrowshahi, J. S., *Indian J. Chem., Sect. B* **1990**, *29B*, 304.
29. Moriarty, R. M.; Khosrowshahi, J. S.; Prakash, O., *Tetrahedron Lett.* **1985**, *26*, 2961.
30. Moriarty, R. M.; Prakash, O.; Musallam, H. A.; Mahesh, V. K., *Heterocycles* **1986**, *24*, 1641.
31. Moriarty, R. M.; Penmasta, R.; Prakash, I., *Tetrahedron Lett.* **1987**, *28*, 877.
32. Ochiai, M.; Oshima, K.; Ito, T.; Masaki, Y.; Shiro, M., *Tetrahedron Lett.* **1991**, *32*, 1327.
33. Koser, G. F.; Wettach, R. H., *J. Org. Chem.* **1977**, *42*, 1476.
34. Zefirov, N. S.; Zhdankin, V. V.; Dan'kov, Yu. V.; Koz'min, A. S.; Chizhov, O. S., *J. Org. Chem. USSR (Engl. Transl.)* **1985**, *21*, 2252; first report of [hydroxy(mesyloxy)iodo]benzene.
35. Lodaya, J. S.; Koser, G. F., *J. Org. Chem.* **1988**, *53*, 210.
36. Hatzigrigoriou, E.; Varvoglis, A.; Bakola-Christianopoulou, M., *J. Org. Chem.* **1990**, *55*, 315.
37. Koser, G. F.; Lodaya, J. S.; Ray, D. G., III; Kokil, P. B., *J. Am. Chem. Soc.* **1988**, *110*, 2987.
38. Koser, G. F.; Chen, X.; Chen, K.; Sun, G., *Tetrahedron Lett.* **1993**, *34*, 779.
39. Xie, Y.-Y.; Chen, Z.-C., *Synth. Commun.* **2002**, *32*, 1875.
40. Andrews, I. P.; Lewis, N. J.; McKillop, A.; Wells, A. S., *Heterocycles* **1994**, *38*, 713.
41. Martín-Santamaría, S.; Espada, M.; Avendaño, C., *Tetrahedron* **1999**, *55*, 1755.
42. Sánchez, J. D.; Ramos, M. T.; Avendaño, C., *J. Org. Chem.* **2001**, *66*, 5731.
43. Sánchez, J. D.; Ramos, M. T.; Avendaño, C., *Tetrahedron Lett.* **2000**, *41*, 2745.
44. Goff, J. M.; Justik, M. W.; Koser, G. F., *Tetrahedron Lett.* **2001**, *42*, 5597.
45. Xie, Y.-Y.; Chen, Z.-C., *Synth. Commun.* **2001**, *31*, 3145.
46. Xie, Y.-Y.; Chen, Z.-C., *J. Chem. Res. (S)* **2001**, 156.
47. Ochiai, M.; Toyonari, M.; Sueda, T.; Kitagawa, Y., *Tetrahedron Lett.* **1996**, *37*, 8421.
48. Ochiai, M.; Toyonari, M.; Nagaoka, T.; Chen, D.-W.; Kida, M., *Tetrahedron Lett.* **1997**, *38*, 6709.
49. Pike, V. W.; Butt, F.; Shah, A.; Widdowson, D. A., *J. Chem. Soc., Perkin Trans. 1* **1999**, 245.
50. Carroll, M. A.; Pike, V. W.; Widdowson, D. A., *Tetrahedron Lett.* **2000**, *41*, 5393.
51. Kang, S.-K.; Lee, H.-W.; Kim, J.-S.; Choi, S.-C., *Tetrahedron Lett.* **1996**, *37*, 3723.
52. Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S., *J. Org. Chem.* **1996**, *61*, 4720.
53. Xia, M.; Chen, Z.-C., *Synth. Commun.* **1999**, *29*, 2457.
54. Wang, L.; Chen, Z.-C., *Synth. Commun.* **2001**, *31*, 1633.
55. Barton, D. H. R.; Jaszberenyi, J. C.; Shinada, T., *Tetrahedron Lett.* **1993**, *34*, 7191.
56. Barton, D. H. R.; Jaszberenyi, J. C.; Liu, W.; Shinada, T., *Tetrahedron* **1996**, *52*, 14673.
57. Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T., *J. Org. Chem.* **2000**, *65*, 6922.
58. Wuts, P. G. M.; Goble, M. P., *Org. Lett.* **2000**, *2*, 2139.
59. Kirschning, A.; Dräger, G.; Harders, J., *Synlett* **1993**, 289.
60. Kirschning, A.; Domann, S.; Dräger, G.; Rose, L., *Synlett* **1995**, 767.
61. Kirschning, A., *Eur. J. Org. Chem.* **1998**, 2267.
62. Kirschning, A., *J. Org. Chem.* **1995**, *60*, 1228.
63. Kirschning, A., *Justus Liebigs Ann. Chem.* **1995**, 2053.
64. Harders, J.; Garming, A.; Jung, A.; Kaiser, V.; Monenschein, H.; Ries, M.; Rose, L.; Schöning, K.-U.; Weber, T.; Kirschning, A., *Justus Liebigs Ann. Chem.* **1997**, 2125.
65. Bovonsombat, P.; Mc Nelis, E., *Tetrahedron Lett.* **1994**, *35*, 6431.
66. Djuardi, E.; Bovonsombat, P.; Mc Nelis, E., *Tetrahedron* **1994**, *50*, 11793.
67. Bovonsombat, P.; Mc Nelis, E., *Tetrahedron Lett.* **1993**, *34*, 4277.
68. Herault, X.; Mc Nelis, E., *Tetrahedron* **1996**, *52*, 10267.
69. Bovonsombat, P.; Mc Nelis, E., *Tetrahedron Lett.* **1993**, *34*, 8205.
70. Bovonsombat, P.; Mc Nelis, E., *Synth. Commun.* **1995**, *25*, 1223.
71. Marchand, A. P.; Rajagopal, D.; Burritt, A.; Bott, S. G.; Watson, W. H.; Sun, D., *Tetrahedron* **1995**, *51*, 11673.
72. Djuardi, E.; Mc Nelis, E., *Tetrahedron Lett.* **1999**, *40*, 7193.
73. Bovonsombat, P.; Mc Nelis, E., *Tetrahedron Lett.* **1992**, *33*, 4123.
74. Bovonsombat, P.; Mc Nelis, E., *Synth. Commun.* **1992**, *22*, 2361.
75. Tuncay, A.; Anaclerio, B. M.; Zolodz, M.; Suslick, K. S., *Tetrahedron Lett.* **1999**, *40*, 599.
76. Prakash, O.; Kumar, D.; Saini, R. K.; Singh, S. P., *Tetrahedron Lett.* **1994**, *35*, 4211.
77. Papoutsis, I.; Spyroudis, S.; Varvoglis, A., *J. Heterocycl. Chem.* **1996**, *33*, 579.
78. Papoutsis, I.; Spyroudis, S.; Varvoglis, A., *Tetrahedron Lett.* **1996**, *37*, 913.
79. Papoutsis, I.; Spyroudis, S.; Varvoglis, A.; Raptopoulou, C. P., *Tetrahedron* **1997**, *53*, 6097.
80. Papoutsis, I.; Spyroudis, S.; Varvoglis, A., *Tetrahedron* **1998**, *54*, 1005.
81. Bovonsombat, P.; Mc Nelis, E., *Synthesis* **1993**, 237.
82. Bovonsombat, P.; Djuardi, E.; Mc Nelis, E., *Tetrahedron Lett.* **1994**, *35*, 2841.
83. Coats, S. J.; Wasserman, H. H., *Tetrahedron Lett.* **1995**, *36*, 7735.
84. Yang, R.-Y.; Dai, L.-X., *Synth. Commun.* **1994**, *24*, 2229.
85. Xia, M.; Chen, Z.-C., *Synth. Commun.* **1997**, *27*, 1315.
86. Xia, M.; Chen, Z.-C., *Synth. Commun.* **1997**, *27*, 1301.
87. Sun, L.; Li, P.; Zhao, K., *Tetrahedron Lett.* **1994**, *35*, 7147.
88. Prakash, O.; Tanwar, M. P., *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1168.
89. Kumar, D.; Singh, O. V.; Prakash, O.; Singh, S. P., *Synth. Commun.* **1994**, *24*, 2637.
90. Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Thomas, J.-L., *Tetrahedron Lett.* **1998**, *39*, 881.
91. Lee, K.-H.; Ko, K.-Y., *Bull. Korean Chem. Soc.* **2002**, *23*, 1505.

92. Varma, R. S.; Kumar, D., *Tetrahedron Lett.* **1998**, *39*, 9113.
93. De, S. K.; Mallik, A. K., *Tetrahedron Lett.* **1998**, *39*, 2389.
94. Moriarty, R. M.; Vaid, R. K.; Ravikumar, V. T.; Vaid, B. K.; Hopkins, T. E., *Tetrahedron* **1988**, *44*, 1603.
95. Fadnavis, N. W.; Vadivel, S. K.; Sharfuddin, M.; Bhalerao, U. T., *Tetrahedron: Asymmetry* **1997**, *8*, 4003.
96. Muraki, T.; Togo, H.; Yokoyama, M., *J. Chem. Soc., Perkin Trans. 1* **1999**, 1713.
97. Zhdankin, V. V.; Maydanovych, O.; Herschbach, J.; Bruno, J.; Matveeva, E. D.; Zefirov, N. S., *J. Org. Chem.* **2003**, *68*, 1018.
98. Zhdankin, V. V.; Maydanovych, O.; Herschbach, J.; Bruno, J.; Matveeva, E. D.; Zefirov, N. S., *Tetrahedron Lett.* **2002**, *43*, 2359.
99. De, S. K.; Mallik, A. K., *Indian J. Chem., Sect. B* **1997**, *36B*, 536.
100. Wirth, T.; Hirt, U. H., *Synthesis* **1999**, 1271.
101. Ray, D. G., III; Koser, G. F., *J. Am. Chem. Soc.* **1990**, *112*, 5672.
102. Rabah, G. A.; Koser, G. F., *Tetrahedron Lett.* **1996**, *37*, 6453.
103. Hirt, U. H.; Schuster, M. F. H.; French, A. N.; Wiest, O. G.; Wirth, T., *Eur. J. Org. Chem.* **2001**, 1569.
104. Hirt, U. H.; Spingler, B.; Wirth, T., *J. Org. Chem.* **1998**, *63*, 7674.
105. Wirth, T.; Hirt, U. H., *Tetrahedron: Asymmetry* **1997**, *8*, 23.

Isopropyldiphenylsulfonium Tetrafluoroborate[1]

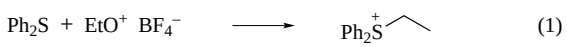


[1660-43-7] $C_{15}H_{17}BF_4S$ (MW 316.20)

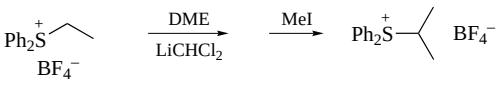
InChI = 1/C15H17S.BF4/c1-13(2)16(14-9-5-3-6-10-14)15-11-7-4-8-12-15;2-1(3,4)5/h3-13H,1-2H3;/q+1;-1
InChIKey = OYVGOJMOYZVZFZ-UHFFFAOYAS

(transformation of carbonyls to *gem*-dimethyloxiranes;[2] conversion of α,β-unsaturated systems[3] and diene esters[4] to geminal substituted cyclopropanes)

Preparative Methods: this reagent is not commercially available and must be made prior to use. The ylide isopropylidenediphenylsulfurane, obtained by deprotonation with an appropriate base, is usually formed in situ and used immediately because of its extremely low stability.[2] Two methods have been reported for the preparation of the sulfurane. Ethyldiphenylsulfonium tetrafluoroborate (formed by the reaction of diphenyl sulfide with triethyloxonium tetrafluoroborate, eq 1) is suspended in a solution of DME. The ylide is formed by addition of $LiCHCl_2$ at −70 °C and reacted with MeI (1.1 equiv). The desired sulfonium salt precipitates from solution. The isopropylidenediphenylsulfurane is formed by addition of LDA to this suspension at −78 °C (eq 2).[2]



(1)



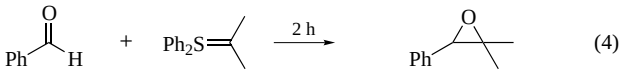
(2)

A second, but less efficient, method of preparation involves the reaction of diphenyl sulfide, $AgBF_4$, and neat isopropyl iodide (eq 3).[2]

(3)

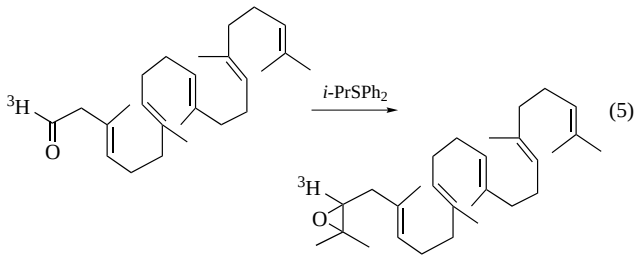
Three different base/solvent systems have been used to generate the isopropylidenediphenylsulfurane ylide: DME/$LiCHCl_2$, *t*-BuOK/THF,[5] and PhLi/THF.[6] All methods have proven equally efficient. Different diastereomer ratios have been obtained with the *t*-BuOK/THF method compared to the other systems.[7]

Reaction with Carbonyls to Form Oxiranes. Addition of 1 equiv of benzaldehyde to a solution of the ylide, formed as described above, in DME at −60 °C results in the formation of the oxirane (eq 4) in 75–80% isolated yield.[2] Ketones may also react in good yields, but reaction times are somewhat longer.



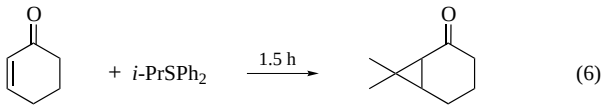
(4)

Van Tamelen et al.[8] used isopropylidenediphenylsulfurane to synthesize radiolabeled 4-norsqualene 2,3-oxide (eq 5) and homosqualene oxide.



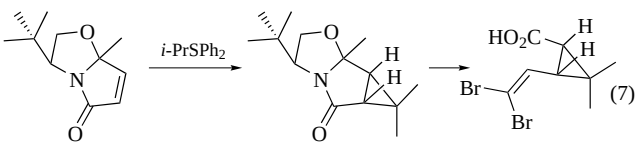
(5)

Reactions with α,β-Unsaturated Compounds. If the carbonyl is α,β-unsaturated, reaction takes place at the alkene via addition/substitution to form *gem*-dimethyl-substituted cyclopropanes. For example, the *gem*-disubstituted cyclopropane was prepared from cyclohexenone in 74% yield (eq 6).[9]



(6)

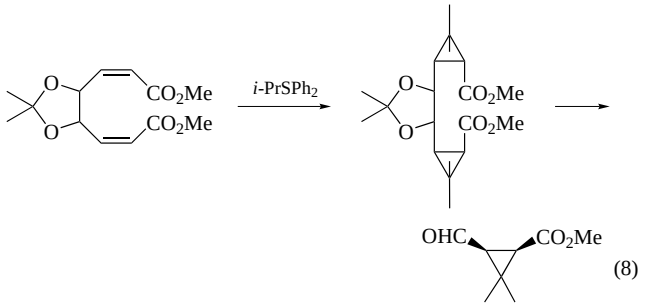
Meyers et al. have reacted the ylide with a chiral bicyclic lactam to yield a tricyclic *gem*-disubstituted cyclopropane intermediate which, after four steps, gave deltamethric acid whose esters act as very potent insecticides (eq 7).[10]



(7)

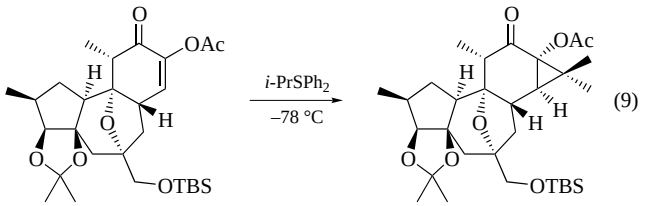
endo:*exo* >200:1 Deltamethric acid

In 1988, Krief et al. used isopropylidenediphenylsulfurane to synthesize (1*R*,3*S*),*cis*-hemicaronic aldehyde, a precursor to the (1*R*,3*S*),*cis*-dibromovinylchrysanthemic acid constituent of deltamethrin (eq 8).[6,11]



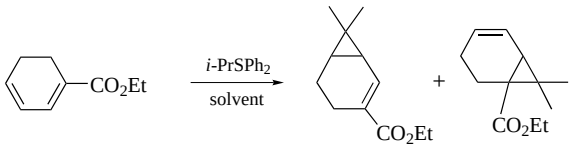
(8)

Wender et al. in 1989 used the ylide to synthesize an essential intermediate in the synthesis of phorbol (eq 9), a tumor promoter.[12]



(9)

Reaction with Diene Esters. Rapoport et al. developed an elegant synthesis of the carene ring system via reaction of 1-ethoxycarbonyl-1,3-cyclohexadiene with isopropylidenediphenylsulfurane (eq 10).[4] The regiochemistry of the cyclopropane formation depends upon the solvent used in the reaction. This dependency of the regioisomer distribution provides a convenient route to either of the two carene ring systems.



(10)

Solvent	Ratio
DME	4:1
THF	1:2

1. Trost, B.; Melvin, L. S., Jr. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic: New York, 1975.
2. Corey, E. J.; Jautelat, M.; Oppolzer, W., *Tetrahedron Lett.* **1967**, 2325.
3. Krief, A.; Dumont, W.; Pasau, P.; Lecomte, P., *Tetrahedron* **1989**, *45*, 3039.
4. Tang, C. B. F.; Rapoport, H., *J. Org. Chem.* **1973**, *38*, 2806.
5. Corey, E. J.; Chaykovsky, M., *J. Am. Chem. Soc.* **1965**, *87*, 1353.
6. Nadeau, R. G.; Hanzlik, R. P., *Methods Enzymol.* **1969**, *15*, 346.
7. Krief, A.; Lecomte, P.; Demonte, J. P.; Dumont W., *Synthesis* **1990**, 275.
8. Van Tamelen, E. E.; Pedlar, A. D.; Li, E.; James, D. R., *J. Am. Chem. Soc.* **1977**, *99*, 6778.
9. Corey, E. J.; Jautelat, M., *J. Am. Chem. Soc.* **1967**, *89*, 3912.
10. Meyers, A. I.; Romo, D., *Tetrahedron Lett.* **1989**, *30*, 1745.
11. Krief, A.; Dumont, W., *Tetrahedron Lett.* **1988**, *29*, 1083.
12. Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D., *J. Am. Chem. Soc.* **1989**, *111*, 8957.

Tony Durst & Robert N. Ben
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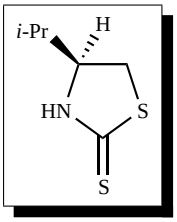
(*S*)-4-Isopropylthiazolidine-2-thione



[76186-04-4] $C_6H_{11}NS_2$ (MW 161.003)

InChI = 1/C6H11NS2/c1-4(2)5-3-9-6(8)7-5/h4-5H,3H2,1-2H3,(H,7,8)/t5-/m1/s1/f/h7H

InChIKey = CWIZUGZKLJDJLE-CMTRKUPJDL

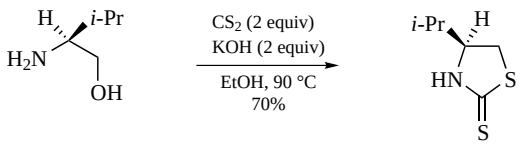
(reagent used as an excellent and convenient chiral auxiliary for several asymmetric C–C bond formation reactions)

Physical Data: mp 67–68 °C ($CHCl_3$); 98.6% ee [HPLC (equipped with chiral packed column) analysis], $[\alpha]_{22}^{D}$ –36.8 ° (c 1.16, $CHCl_3$), λ_{max} 280.4 nm (ε 1.55 × 10^4, $CHCl_3$).[1]

Solubility: sol CH_2Cl_2, $CHCl_3$, THF, MeCN, Et_2O, and AcOEt.

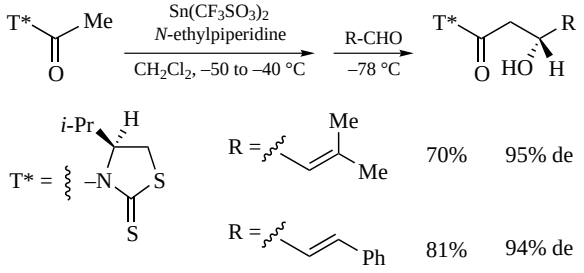
Form Supplied in: colorless needles; readily prepared.

Preparation: to a solution of (*S*)-valinol (10.3 g, 0.1 mol) and CS_2 (15.2 g, 0.2 mol) in EtOH (40 mL) was added dropwise a solution of KOH (13.2 g, 0.24 mol) in EtOH (40 mL) and water (7 mL) with stirring under ice-cooling. The mixture was stirred at 90 °C for 3 days under N_2 before the excess of EtOH was removed *in vacuo*. The residual water solution was acidified (pH 2–2.5) with 20% HCl under ice-cooling and then extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and then evaporated in vacuo to give an oily residue. The residue was chromatographed on a silica gel column with *n*-hexane–AcOEt (2 : 1) to obtain (*S*)-4-isopropyl-1,3-thiazolidine-2-thione [(*S*)-IPTT] (11.2 g, 70% yield) as colorless needles from CH_2Cl_2 (eq 1).[1] The reagent can be stored without decomposition in a refrigerator more than 1 year.



(1)

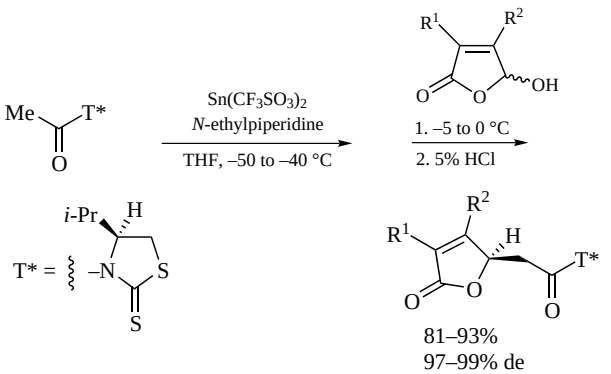
Diastereoselective Aldol-type Reactions Using Aldehydes. Treatment of (*S*)-IPTT with various acid chlorides in the presence of an amine base gave readily the corresponding *N*-acyl (*S*)-IPTT amides in an excellent yield, each as a yellow crystalline compound. Diastereoselective aldol-type reactions of *N*-acetyl (*S*)-IPTT with *trans*-cinnamaldehyde or 3-methyl-2-butenylaldehyde employing tin(II) trifluoromethanesulfonate[2] and *N*-ethylpiperidine[2] in anhydrous CH_2Cl_2 at −50 to −40 °C [for enolization of *N*-acetyl (*S*)-IPTT] and then at −78 °C (for aldol-type reaction) under argon afforded the corresponding aldol products in 95% de (70% total yield of both diastereoisomers) or in 94% de (81% total yield of both diastereoisomers), respectively (eq 2).[1]



(2)

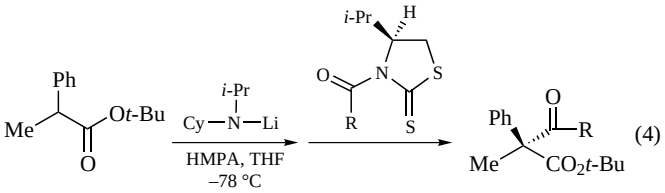
Chromatographic separation of both diastereomers on a silica gel column can be readily monitored by their yellow color due to the 3-acyl-1,3-thiazolidine-2-thione structure [UV λ_{max} 415 nm (ε 61, *n*-hexane)]. The chiral auxiliary, (*S*)-IPTT, can be smoothly removed (recovered) from the aldol product by methanolysis with MeOH in the presence of K_2CO_3 giving the methyl ester, and by aminolysis with organic amines (alkyl amines, benzyloxyamine, imidazole, etc.) giving the amides.[3] This reaction can also be monitored by disappearance of the original yellow color of *N*-acyl (*S*)-IPTT amides.[3] This highly diastereoselective acetatealdol reaction was exploited for asymmetric synthesis of various natural products such as the potent immunosuppressant ISP-I,[4] spongistatin 1,[5] (−)-mycothiazole,[6] aurisides and callipeltosides,[7] phorboxazole B,[8] spiruchostain A,[9] *seco*-proansamitocin,[10] ripostatin A and B,[11] and solandelactones E and F.[12]

Diastereoselective Aldol-type Reaction Using γ-Hydroxybutenolides. The chiral tin(II) enolate was prepared by treatment of *N*-acetyl (*S*)-IPTT with tin(II) trifluoromethanesulfonate in the presence of *N*-ethylpiperidine in THF at −50 to −40 °C for 3 h. After reaction of the tin(II) enolate with a solution of several γ-hydroxybutenolides in dry THF at −5 to 0 °C for 2 h, the reaction mixture was treated with 5% HCl to give the chiral crystalline γ-alkylated butenolides in 81–93% yields and in 97–99% de (eq 3).[13]



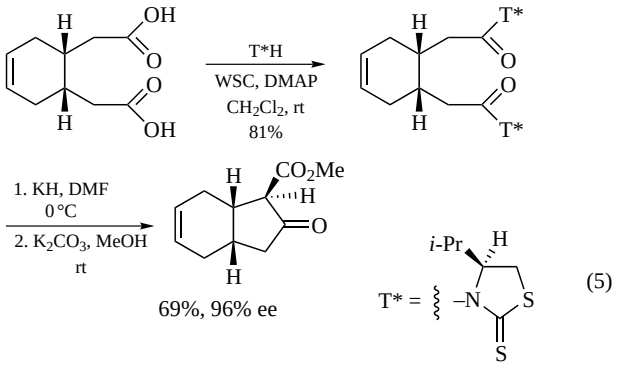
(3)

Enantioselective Claisen-type Acylation and Dieckmann-Type Annulation. To a solution of lithium *N*-isopropylcyclohexylamide (LICA) prepared from *n*-butyllithium and *N*-isopropylcyclohexylamine in THF was added dropwise a solution of *tert*-butyl 2-phenylpropionate in THF at −78 °C under N_2 with stirring. Hexamethylphosphoric triamide (HMPA) was added and the mixture was stirred at −78 °C for 30 min. After addition of a solution of *N*-acetyl (or *N*-butyryl) (*S*)-IPTT amide in THF at −78 °C, the mixture was stirred at the same temperature for 15 min to give the acetyl or butyryl derivative in 77% yield and 96% ee or in 75% yield and 95% ee, respectively (eq 4).[14]



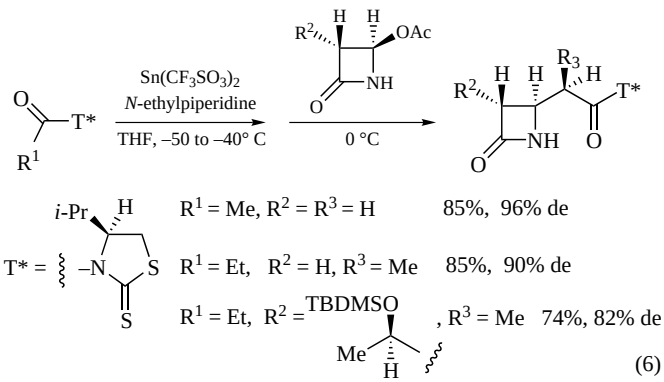
(4)

The enantioselective Dieckmann-type annulation was carried out as follows. *cis*-Cyclohex-4-ene-1,2-bisacetic (*S*)-IPTT diamide was added to a suspension of 35% KH in mineral oil and DMF under ice-cooling. After being stirred at the same temperature for 3 h, the resultant bicyclic (*S*)-IPTT amide product was subjected to methanolysis with K_2CO_3 in MeOH gave the methyl ester in 69% overall yield and in 96% ee (eq 5).[14]



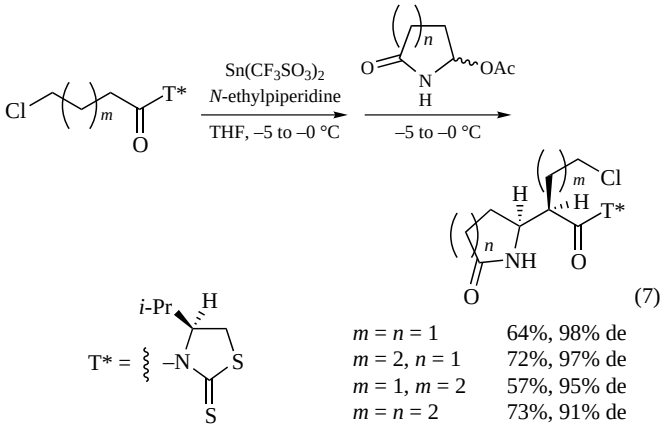
(5)

Diastereoselective Alkylation onto Cyclic Acyl Imines. ω-Acetoxylactams can be utilized as the corresponding cyclic acylimines in a reaction medium employing a Lewis acid [e.g., $Sn(CF_3SO_3)_2$] and an amine base (e.g., *N*-ethylpiperidine). Thus, asymmetric alkylations onto 4-acetoxyazetidin-2-one or chiral 3-substituted 4-acetoxyazetidin-2-one using the chiral tin(II) enolate of *N*-acetyl or *N*-propionyl (*S*)-IPTT amide were successfully performed in THF at 0 °C for 1 h. These reactions gave chiral C4-alkylated azetidin-2-ones in 85% yield (96% de), 85% yield (90% de), and 74% yield (82% de), respectively (eq 6). This asymmetric reaction was efficiently applied to development of a novel 1β-methylcarbapenem antibiotic, "Biapenem".[15]



(6)

An extremely short asymmetric synthesis of the bicyclic alkaloids having a nitrogen atom ring juncture was established based on the following asymmetric alkylation reactions. Namely, tin(II) trifluoromethanesulfonate was dissolved in THF under argon atmosphere at room temperature. To the solution cooled at −5 °C was added successively *N*-ethylpiperidine and 3-(4-chlorobutyryl)- or 3-(5-chlorovaleryl)-(*S*)-IPTT in THF followed by stirring at −5 to 0 °C for 4 h to form the corresponding tin(II) enolate. To the tin(II) enolate was added a ca. 1.0 M solution of 5-acetoxy-2-pyrrolidinone (n = 1) or a ca. 0.8 M solution of 6-acetoxy-2-piperidinone (n = 2) in THF at −5 °C, and the mixture was then stirred at −5 to 0 °C for 2 h to give the C5-alkylated 2-pyrrolidinones or C6-alkylated piperidinones in 57–73% yields and in 91–98% de (eq 7). Reductive annulation of these chiral products with $LiAlH_4$ in THF gave bicyclic alkaloids such as (−)-trachelanthamidine, (−)-tashiromine, and (+)-epilupinine, respectively.[16]



(7)

$m = n = 1$	64%, 98% de
$m = 2$, $n = 1$	72%, 97% de
$m = 1$, $m = 2$	57%, 95% de
$m = n = 2$	73%, 91% de

Related Reagents. (*S* or *R*)-4-Ethyl-1,3-thiazolidine-2-thione;[1] (*S* or *R*)-4-Methoxycarbonyl-1,3-thiazolidine-2-thione;[17] (*S*)-4-Methoxycarbonyl-1,3-thiazolidine-2-selenone;[18] (*S*)-4-Methoxycarbonyl-1,3-oxazolidine-2-thione;[18] (*S*)-4-Isopropyl-1,3-oxazolidine-2-thione;[19] (*S* or *R*)-4-Ethyl-1,3-oxazolidine-2-thione;[19] (*R*)-4-methyl-(*S*)-5-Phenyl-1,3-oxazolidine-2-thione;[19] (*S*)-4-(phenylmethyl)-1,3-thiazolidine-2-thione.[20]

1. (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E., *J. Org. Chem.* **1986**, *51*, 2391. (b) Fujita, E.; Nagao, Y. *In Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1989; Vol. 45, p 1.
2. Iwasawa, N.; Mukaiyama, T., *Chem. Lett.* **1983**, 297.
3. Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; Fujita, E., *Tetrahedron Lett.* **1980**, *21*, 841.
4. Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y., *Tetrahedron Lett.* **1995**, *36*, 2097.
5. Zuev, D.; Paquette, L. A., *Org. Lett.* **2000**, *2*, 679.
6. Sugiyama, H.; Yokokawa, F.; Shioiri, T., *Org. Lett.* **2000**, *2*, 2149.
7. Romero-Ortega, M.; Colby, D. A.; Olivo, H. F., *Tetrahedron Lett.* **2002**, *43*, 6439.
8. Paterson, I.; Steven, A.; Luckhurst, C. A., *Org. Biomol. Chem.* **2004**, *2*, 3026.
9. Yurek-George, A.; Habens, F.; Brimmell, M.; Packham, G.; Ganesan, A., *J. Am. Chem. Soc.* **2004**, *126*, 1030.
10. Frenzel, T.; Brünjes, M.; Quitschalle, M.; Kirschning, A., *Org. Lett.* **2006**, *8*, 135.
11. Kujat, C.; Bock, M.; Kirschning, A., *Synlett* **2006**, 419.
12. White, J. D.; Martin, W. H. C.; Lincoln, C.; Yang, J., *Org. Lett.* **2007**, *9*, 3481.
13. Nagao, Y.; Dai, W. M.; Ochiai, M.; Shiro, M., *J. Org. Chem.* **1989**, *54*, 5211.
14. Nagao, Y.; Hagiwara, Y.; Tohjo, T.; Hasegawa, Y.; Ochiai, M.; Shiro, M., *J. Org. Chem.* **1988**, *53*, 5983.
15. (a) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E., *J. Am. Chem. Soc.* **1986**, *108*, 4673. (b) Nagao, Y.; Kumagai, T.; Abe, T.; Ochiai, M.; Taga, T.; Machida, K.; Inoue, Y., *J. Chem. Soc., Chem. Commun.* **1987**, 602. (c) Nagao, Y.; Abe, T.; Shimizu, H.; Kumagai, T.; Inoue, Y., *J. Chem. Soc., Chem. Commun.* **1989**, 821. (d) Nagao, Y.; Kumagai, T.; Nagase, Y.; Tamai, S.; Inoue, Y.; Shiro, M., *J. Org. Chem.* **1992**, *57*, 4232. (e) Nagao, Y.; Nagase, Y.; Kumagai, T.; Kuramoto, Y.; Kobayashi, S.; Inoue, Y.; Taga, T.; Ikeda, H., *J. Org. Chem.* **1992**, *57*, 4238. (f) Nagao, Y.; Nagase, Y.; Kumagai, T.; Matsunaga, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y., *J. Org. Chem.* **1992**, *57*, 4243.
16. (a) Nagao, Y.; Dai, W. M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E., *J. Am. Chem. Soc.* **1988**, *110*, 289. (b) Nagao, Y.; Dai, W. M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E., *J. Org. Chem.* **1990**, *55*, 1148. (c) Nagao, Y.; Dai, W. M.; Ochiai, M.; Shiro, M., *Tetrahedron* **1990**, *46*, 6361. (d) Nagao, Y.; Matsunaga, H.; Kumagai, T.; Inoue, Y., *J. Chem. Soc., Chem. Commun.* **1992**, *436*. (e) Nagao, Y.; Matsunaga, H.; Kumagai, T.; Inoue, Y.; Miwa, Y.; Taga, T., *J. Chem. Soc., Chem. Commun.* **1992**, 437. (f) Nagao, Y.; Dai, W. M.; Ochiai, M., *Tetrahedron Lett.* **1988**, *29*, 6133.
17. (a) Nagao, Y.; Ikeda, T.; Yagi, M.; Fujita, E.; Shiro, M., *J. Am. Chem. Soc.* **1982**, *104*, 2079. (b) Nagao, Y.; Ikeda, T.; Inoue, T.; Yagi, M.; Shiro, M.; Fujita, E., *J. Org. Chem.* **1985**, *50*, 4072.
18. Nagao, Y.; Kumagai, T.; Takao, S.; Abe, T.; Ochiai, M.; Inoue, Y.; Taga, T.; Fujita, E., *J. Org. Chem.* **1986**, *51*, 4737.
19. (a) Nagao, Y.; Kumagai, T.; Yamada, S.; Fujita, E.; Inoue, Y., *J. Chem. Soc. Perkin Trans. 1* **1985**, 2361. (b) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E., *J. Chem. Soc., Chem. Commun.* **1985**, 1418. (c) Nagao, Y.; Inoue, T.; Hashimoto, K.; Hagiwara, Y.; Ochiai, M.; Fujita, E., *J. Chem. Soc., Chem. Commun.* **1985**, 1419.
20. Delaunary, D.; Toupet, L.; Le Corre, M., *J. Org. Chem.* **1995**, *60*, 6604.

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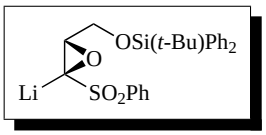
L

(1*R*,2*S*)-1-Lithio-1-phenylsulfonyl-2-[(*tert*-butyldiphenyl)silyl]oxymethyloxirane



[181208-42-4] $C_{25}H_{27}LiO_4SSi$ (MW 458.08)

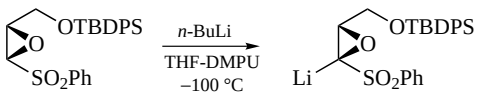
InChI = 1/C25H27O4SSi.Li/c1-25(2,3)31(21-15-9-5-10-16-21, 22-17-11-6-12-18-22)28-19-23-24(29-23)30(26,27) 20-13-7-4-8-14-20;/h4-18,23H,19H2,1-3H3;/t23-;/ m0./s1/rC25H27LiO4SSi/c1-24(2,3)32(21-15-9-5-10-16-21,22-17-11-6-12-18-22)29-19-23-25(26,30-23)31(27,28)20-13-7-4-8-14-20/h4-18,23H,19H2,1-3H3/t23-,25-/m0/s1

InChIKey = DWECMIWJUOLYNJ-DMAZWYCZBE

(oxiranyllithium; oxiranyl anion; nucleophilic epoxide; acyl anion equivalent; epoxy sulfone)

Solubility: soluble in THF, diethyl ether.

Preparative Methods: prepared by lithiation of (1*R*,2*S*)-1-phenylsulfonyl-2-{[(*tert*-butyldiphenyl)silyl]oxymethyl}oxirane (**1**, $[\alpha]_D$ +55.9°, *c* 1.0, $CHCl_3$) (1.0 equiv) in THF (0.15 M solution) with *n*-BuLi (1 equiv, 1.6 M solution in hexane) in the presence of DMPU or hexamethylphosphoramide (HMPA) (3.0 equiv) at −100 °C under argon. Deprotonation is completed within a few minutes (eq 1).[1]



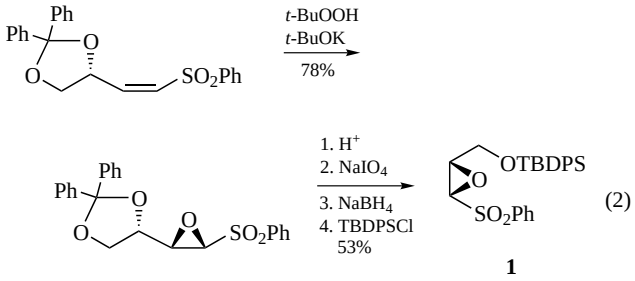
(1)

1

Handling, Storage, and Precautions: the oxiranyllithium is very unstable, even at −100 °C under argon, and should be reacted with electrophiles immediately. The reagent is also conformationally unstable and slowly isomerizes to the *trans*-isomer when addition of an electrophile is delayed (about 5% isomerization after 20 min at −100 °C). Elevated temperatures (>−78 °C) cause rapid decomposition.[1,2]

Introduction. Although epoxides are widely recognized as extremely versatile synthetic intermediates in view of their electrophilic nature, the reaction of an epoxide as a nucleophile, i.e. an oxiranyl anion, is less common. Recently, cumulative studies on the chemistry of oxiranyl anions have appeared and some aspects of the anions have been discussed.[3,4]

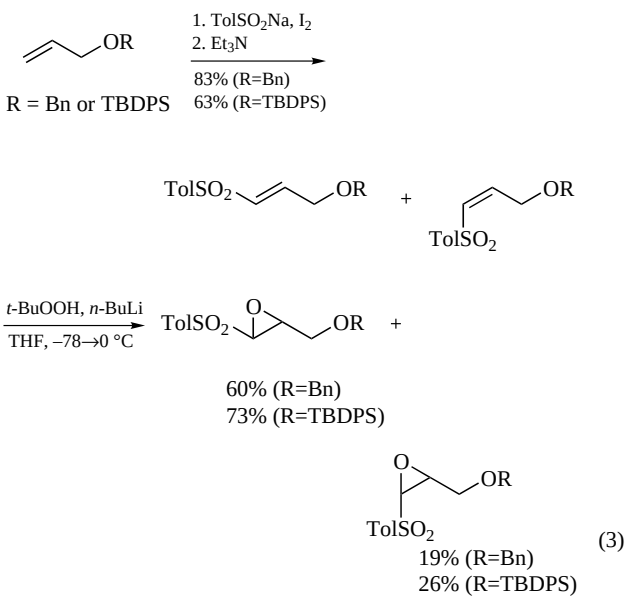
Preparation of (1*R*,2*S*)-1-Phenylsulfonyl-2-{[(*tert*-butyldiphenyl)silyl]oxymethyl}oxirane and Related Compounds. Epoxidation of (*Z*)-vinyl sulfone, which is available from the Peterson olefination of (*S*)-*O*-pentylideneglyceraldehyde[5] and phenyl trimethylsilylmethyl sulfone[6] in three steps (40% overall yield), with *t*-BuOOH/*t*-BuOK in THF gives epoxy sulfone (eq 2). Deprotection of the ketal group and recrystallization affords an optically pure epoxy diol, which is then treated with sodium periodate followed by sodium borohydride to give an alcohol. Protection of the resulting alcohol as its silyl ether yields (1*R*, 2*S*) -1- phenylsulfonyl-2-{[(*tert*-butyldiphenyl)silyl]oxymethyl} oxirane (**1**).[7] Its enantiomer is available in the same manner starting from (*R*)-isopropylideneglyceraldehyde.[8]



(2)

1

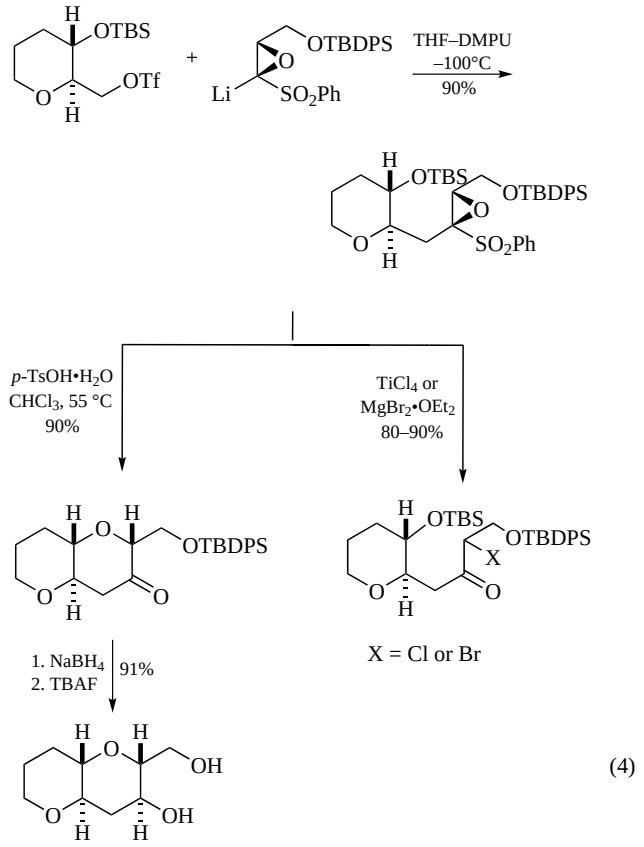
Racemic epoxy sulfone derivatives are easily prepared from allyl ethers by reaction with sodium *p*-toluenesulfinate in the presence of iodine followed by treatment with triethylamine, separation of *E*- and *Z*-isomers, and epoxidation with *t*-BuOOH and *n*-BuLi in THF (eq 3).[2]



(3)

Reaction of Sulfonyl-stabilized Oxiranyllithiums. Reaction of sulfonyl-stabilized oxiranyllithiums with primary alkyl halides gives acceptable yields of products.[1] More reactive alkyl triflates give generally better yields but, due to the instability of oxiranyllithiums, yields are often not reproducible when electrophiles

are added to a solution of the preformed oxiranyllithiums. It is recommended that the alkylation reaction be carried out by an in situ trapping method.[2] Treatment of a solution of epoxy sulfone (1.0 equiv) and triflate (1.5 equiv) in THF-DMPU (or HMPA) at −100 °C under argon with *n*-BuLi (1.0 equiv) followed by stirring for 30 min affords the coupled product in high yield (eq 4).[9] The product can be converted to a tetrahydropyranone derivative by exposure to *p*-toluenesulfonic acid. The strong electron-withdrawing ability of the sulfonyl group works against the adjacent C–O bond-breaking in an acid-catalyzed epoxide ring-opening process and, consequently, favors the 6-*endo* mode pathway which yields the tetrahydropyranone after elimination of phenylsulfinic acid. Reaction with a halogenated metal Lewis acid yields a halo ketone instead of a cyclization product (eq 4).[10] These reactions demonstrate that the oxiranyllithium reagent serves as a functionalized acyl anion equivalent and a three-carbon building block.

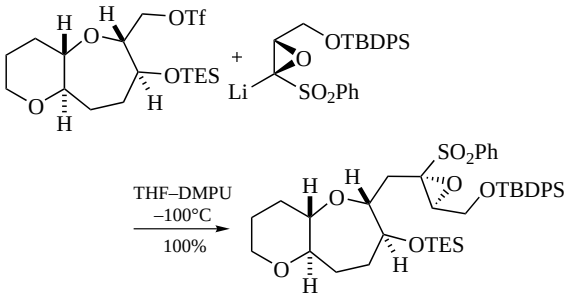


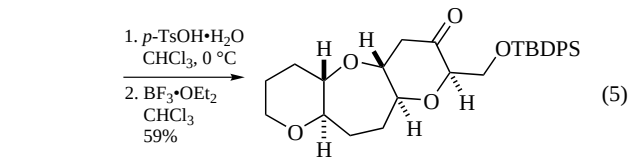
(4)

Reiterative application of this protocol has allowed the stereocontrolled construction of polytetrahydropyrans[9,10] and polycyclic ethers containing six- and seven-membered rings (eq 5).[7]

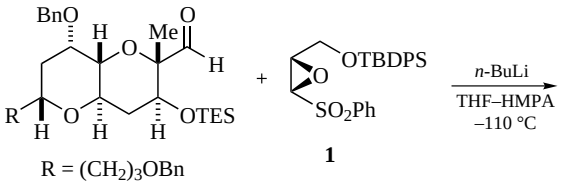
Reaction of the oxiranyllithium with aldehydes is also carried out by an in situ trapping method at very low temperatures in order to avoid decomposition of the reagent. Its applicability to a complex situation has been demonstrated in a synthesis of hemibrevetoxin B (eq 6).[11,12] It is noteworthy that deprotonation of **1** by *n*-BuLi is much faster than butyl addition to the aldehyde.

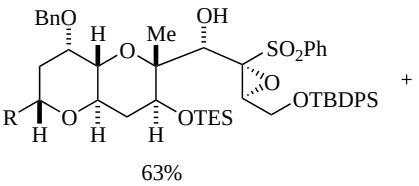
While alkylation of sulfonyl-stabilized oxiranyllithiums with primary alkyl triflates proceeds in high yield, the reaction towards epoxides is relatively slow (~2 h) and the decomposition of oxiranyllithium is marked, such that it decreases the yield, especially in the case of a *Z*-isomer (eq 7 and 8).[2] Addition of boron trifluoride diethyl etherate promotes this epoxide-epoxide coupling reaction. One of the diastereoisomers of eq 8 has been elaborated via 5-*endo* cyclization into a marine tetrahydrofuran isolated from a brown alga.[13]

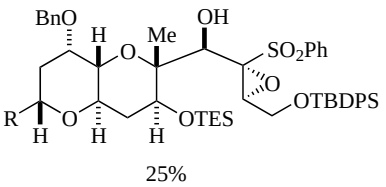




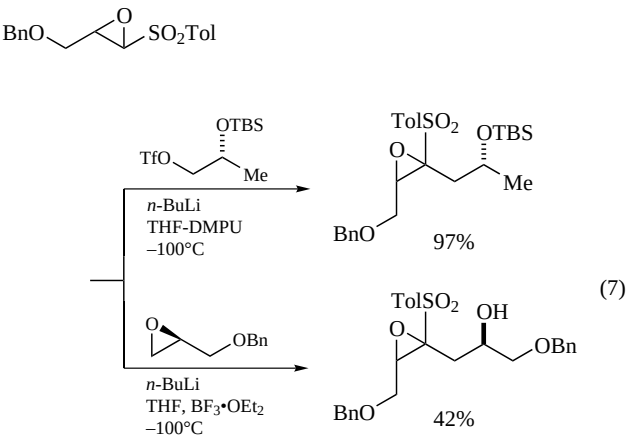
(5)





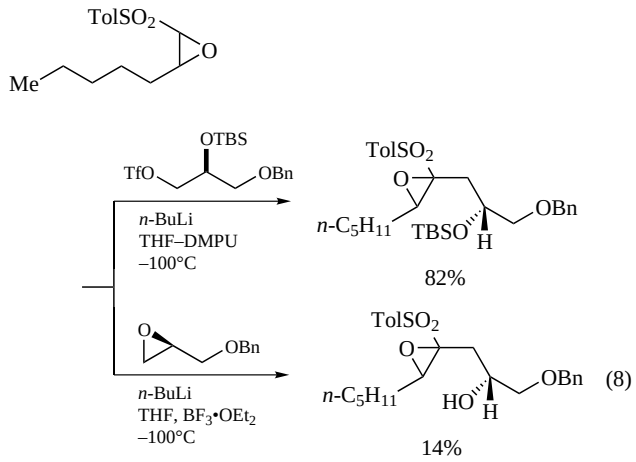


(6)

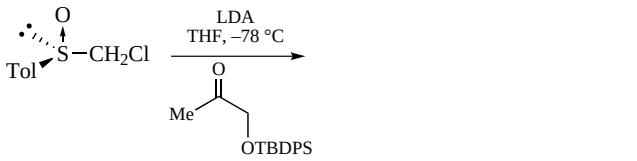


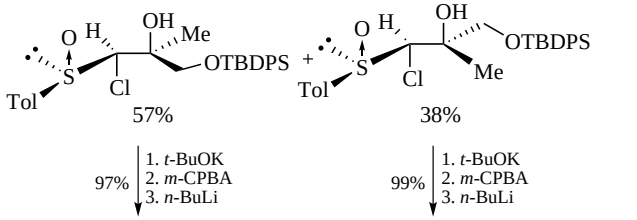
(7)

Related Reagents. Optically active trisubstituted sulfonyl-stabilized oxiranyllithiums can be generated by deprotonation of the corresponding epoxy sulfones[14] (eq 9). Due to the diminished reactivity of the reagents by steric hindrance, the reaction with triflates requires HMPA to obtain a high yield of product (eq 10).[12]

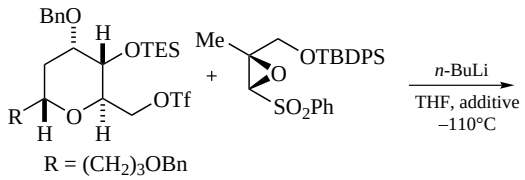


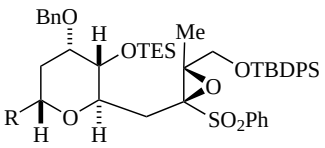
(8)





(9)





(10)

HMPA: 90%
DMPU: 57%

1. (a) Ashwell, M.; Clegg, W.; Jackson, R. F. W., *J. Chem. Soc., Perkin Trans. 1* **1991**, 897. (b) Dunn, S. F. C.; Jackson, R. F. W., *J. Chem. Soc., Perkin Trans. 1* **1992**, 2863.
2. Mori, Y.; Yaegashi, K.; Iwase, K.; Yamamori, Y.; Furukawa, H., *Tetrahedron Lett.* **1996**, *37*, 2605.
3. Satoh, T., *Chem. Rev.* **1996**, *96*, 3303.
4. Mori, Y. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1997, Vol. 17, p 183.
5. Schmid, C. R.; Bradley, D. A., *Synthesis* **1992**, 587.
6. Craig, D.; Ley, S. V.; Simpkins, N. S.; Whitham, G. H.; Prior, M. J., *J. Chem. Soc., Perkin Trans. 1* **1985**, 1949.
7. Mori, Y.; Yaegashi, K. Furukawa, H., *Tetrahedron* **1997**, *53*, 12917.
8. Schmid, C. R.; Bryant, J. D.; Dowlatzadeh, M.; Philps, J. L.; Prather, D. E.; Schantz, R. E.; Sear, N. L.; Vianco, C. S., *J. Org. Chem.* **1991**, *56*, 4056.
9. Mori, Y.; Yaegashi, K.; Furukawa, H., *J. Am. Chem. Soc.* **1996**, *118*, 8158.
10. Mori, Y.; Yaegashi, K.; Furukawa, H., *Tetrahedron Lett.* **1999**, *40*, 7239.
11. Mori, Y.; Yaegashi, K.; Furukawa, H., *J. Am. Chem. Soc.* **1887**, *119*, 4557.
12. Mori, Y.; Yaegashi, K.; Furukawa, H., *J. Org. Chem.* **1998**, *63*, 6200.
13. Mori, Y.; Sawada, T.; Furukawa, H., *Tetrahedron Lett.* **1999**, *40*, 731.
14. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K., *J. Org. Chem.* **1989**, *5* **4**, 3130.

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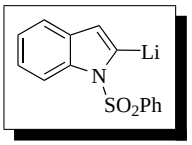
2-Lithio-*N*-phenylsulfonylindole



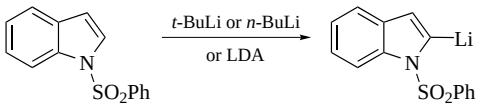
[40900-03-6] $C_{14}H_{10}LiNO_2S$ (MW 263.26)

InChI = 1/C14H10NO2S.Li/c16-18(17,13-7-2-1-3-8-13)15-11-10-12-6-4-5-9-14(12)15;/h1-10H;/rC14H10LiNO2S/c15-14-10-11-6-4-5-9-13(11)16(14)19(17,18)12-7-2-1-3-8-12/h1-10H

InChIKey = FGHIFXKMTBYUOI-NRYADDOCAN

(nucleophilic organolithium reagent useful for addition to ketones, aldehydes, esters, lactones, acid chlorides, anhydrides, nitriles, methyl iodide, halogen sources, and sulfur dioxide; employed in the synthesis of 2-substituted indoles and alkaloids)

Preparative Methods: by deprotonation of *N*-phenylsulfonylindole[1] with *tert*-butyllithium in ether (−12 °C to room temperature),[1] by treatment of *N*-phenylsulfonylindole with butyllithium in THF (−70 °C),[2] and by deprotonation of *N*-phenylsulfonylindole with lithium diisopropylamide in THF (−70 to 5 °C) (eq 1).[3]



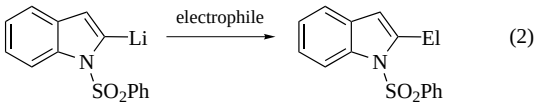
(1)

(1)

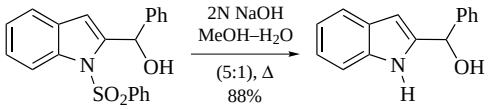
Handling, Storage, and Precautions: the reagent is generated in situ, under anhydrous conditions, in an inert atmosphere,

and used shortly after preparation. The stability in storage is unknown. Precautions for preparation and use are as for other reactive organolithium reagents.

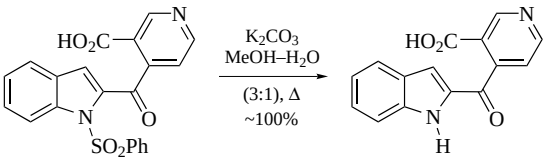
Synthesis of 2-Substituted Indoles. Heteroaromatic compounds such as furan and thiophene are readily metalated at an α-position and the resulting organometallic reagents can be captured by a variety of electrophiles.[4a] *N*-Unsubstituted indoles and pyrroles suffer removal of the acidic N–H, affording ambident nucleophiles[4a] which give rise to mixtures of *C*- and *N*-substituted products upon reaction with electrophiles.[4b] 1-Methylindole can be lithiated at the 2-position to provide 1,2-disubstituted indoles after capture by an electrophile.[5] Difficulties associated with *N*-dealkylation restrict this method to the preparation of 1,2-disubstituted indoles.[1] Substitution at the 1-position of the indole moiety with a readily removable group provides access to 2-substituted indoles. *N*-Phenylsulfonylindole is readily deprotonated (eq 1) to give 2-lithio-*N*-phenylsulfonylindole (**1**) which reacts with electrophiles (eq 2) such as aldehydes,[1] ketones,[1] acid chlorides,[1] carbon dioxide,[1] anhydrides,[1,6] arylsulfonyl chloride,[7] cyanogen bromide,[7] iodine,[7] and sulfur dioxide[2] to give *N*-phenylsulfonyl substituted indolyl-2-carbinols (from aldehydes, ketones), 2-ketones (from acid chlorides, anhydrides), 2-carboxylic acid (from carbon dioxide), 2-sulfones (from arylsulfonyl chlorides), 2-bromide (from cyanogen bromide), 2-iodide (from iodine), and 2-sulfonic acid salt (from sulfur dioxide) in reasonable yields (25–85%). 2-Lithio-*N*-phenylsulfonylindole (**1**) appears to react poorly with alkyl halides. The reaction of (**1**) with ethyl benzoate gives 2-indolyl phenyl ketone (26%), a product of in situ phenylsulfonyl cleavage.[1] Similarly, the reaction of (**1**) with benzonitrile also yields 2-indolyl phenyl ketone (30%).[1] Cleavage of the *N*-phenylsulfonyl group to generate the target 2-substituted indole is readily accomplished with 2N sodium hydroxide in methanol (reflux, eq 3)[1] or potassium carbonate in methanol/water (3:1) at reflux (eq 4).[6]



(1) (2)



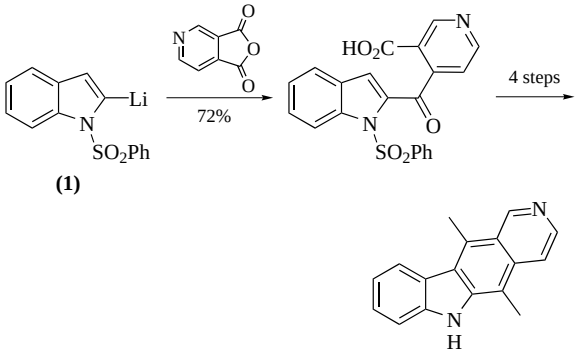
(3)



(4)

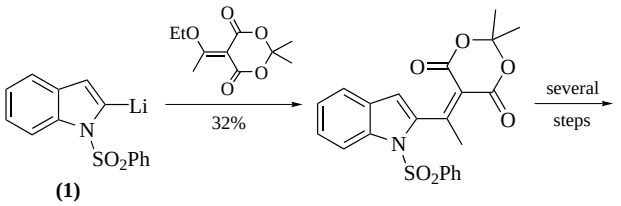
Alkaloid Synthesis. Indole alkaloids such as ellipticine (eq 5)[6] and the genotoxic amine TrpP-1 (eq 6)[8] have been prepared from 2-lithio-*N*-phenylsulfonylindole (**1**).

Related Reagents. A number of indole *N*-protecting groups have been reported to afford variants of 2-lithio-*N*-phenylsulfonylindole which lead to the preparation of 2-substituted products amenable to further synthetic transformation. Table 1 shows a number of removable nitrogen blocking groups in the indole and pyrrole series. In the indole series, (**2a–g**)[1–3,9a–i] readily provide *N*-deprotected 2-substituted indoles. Indolyllithium reagents (**2g**)[1] and (**2h**)[1] are less well explored. In the pyrrole series, (**3a**)[9a] and (**3g**)[10g,h] are problematic due to competitive desulfonylation (**3a**) and silicon migration (**3g**). Pyrrolyllithiums (**3b**),[9a,10a] (**3c**),[9d,10b–d] (**3d**),[10e] and (**3e**)[9h] provide satisfactory yields of 2-substituted pyrroles, although (**3b**)[9a] has been reported to be thermally labile and (**3c**)[9d,10b–d] requires carefully controlled deprotection conditions. Pyrrolyllithium (**3f**) has not been widely examined.[10f]



(1) (5)

54% from (**1**)



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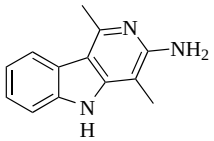

(6)

(2) (3)

X = removable *N*-blocking group

Table 1 *N*-Blocked 2-lithioindoles and *N*-blocked 2-lithiopyrroles

(**2**)	X	Ref.	(**3**)	X	Ref.
a	SO_2Ph	1–3	**a**	SO_2Ph	9a
b	CO_2t-Bu	9a–c	**b**	CO_2-*t*-Bu	9a, 10a
c	SEM	9d	**c**	SEM	9d, 10b–d
d	CO_2^-	9e–g	**d**	CO_2^-	10e
e	CON(*t*-Bu)Li	9h	**e**	CON(*t*-Bu)Li	9h
f	CH_2NMe_2	9i	**f**	NMe_2	10f
g	CH_2OMe	1	**g**	SiR_3	10g,h
h	SiR_3	1			

1. Sundberg, R. J.; Russel, H. F., *J. Org. Chem.* **1973**, *38*, 3324.
2. Graham, S. L.; Hoffman, J. M.; Gautheron, P.; Michelson, S. R.; Scholz, T. H.; Schwam, H.; Shepard, K. L.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Sugrue, M. F., *J. Med. Chem.* **1990**, *33*, 749.
3. (a) Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S., *J. Org. Chem.* **1981**, *46*, 2979. (b) Saulnier, M. G.; Gribble, G. W., *J. Org. Chem.* **1982**, *47*, 757.
4. (a) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: Oxford, 1985; p 261. (b) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: Oxford, 1985; p 245.
5. Shirley, D. A.; Roussel, P. A., *J. Am. Chem. Soc.* **1953**, *75*, 375.
6. (a) Saulnier, M. G.; Gribble, G. W., *J. Org. Chem.* **1982**, *47*, 2810. (b) Gribble, G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M., *J. Org. Chem.* **1992**, *57*, 5891.
7. Ketcha, D. M.; Lieurance, B. A.; Homan, D. F. J.; Gribble, G. W., *J. Org. Chem.* **1989**, *54*, 4350.
8. Hibino, S.; Sugino, E.; Kuwada, T.; Ogura, N.; Sato, K.; Choshi, T., *J. Org. Chem.* **1992**, *57*, 5917.
9. (a) Hasan, I.; Marinelli, E. R.; Lin, L-C. C.; Fowler, F. W.; Levy, A. B., *J. Org. Chem.* **1981**, *46*, 157. (b) Cheng, A. C.; Shulgin, A. T.; Castagnoli, N., Jr., *J. Org. Chem.* **1982**, *47*, 5258. (c) Kline, T., *J. Heterocycl. Chem.* **1985**, *22*, 505. (d) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D., *Chem. Commun.* **1983**, 630. (e) Katritzky, A. R.; Akutagawawa, K., *Tetrahedron Lett.* **1985**, *26*, 5935. (f) Bergman, J.; Venemalm, L., *Tetrahedron Lett.* **1987**, *28*, 3741. (g) Bergman, J.; Venemalm, L., *Tetrahedron Lett.* **1988**, *29*, 2993. (h) Gharpure, M.; Stoller, A.; Bellamy, F.; Firnau, G.; Snieckus, V., *Synthesis* **1991**, 1079. (i) Katritzky, A. R.; Lue, P.; Chen, Y-X., *J. Org. Chem.* **1990**, *55*, 3688.
10. (a) Martina, S.; Enkelmann, V.; Wegner, G.; Schlüter, A.-D., *Synthesis* **1991**, 613. (b) Muchowski, J. M.; Solas, D. R., *J. Org. Chem.* **1984**, *49*, 203. (c) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J., *J. Org. Chem.* **1984**, *49*, 3503. (d) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M., *Tetrahedron* **1986**, *42*, 3723. (e) Katritzky, A. R.; Akutagawawa, K., *Org. Prep. Proced. Int.* **1988**, *20*, 585. (f) Martinez, G. R.; Grieco, P. A.; Srinivasan, C. V., *J. Org. Chem.* **1981**, *46*, 3760. (g) Chadwick, D. J.; Hodgson, S. T., *J. Chem. Soc., Perkin Trans. 1* **1982**, 1833. (h) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M., *J. Org. Chem.*, **1990**, *55*, 6317.

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Lithium Butyl(phenylthio)cuprate[1]

n-BuCu(SPh)Li

[53128-68-0] $C_{10}H_{14}CuLiS$ (MW 236.80)

InChI = 1/C6H6S.C4H9.Cu.Li/c7-6-4-2-1-3-5-6;1-3-4-2;;/h1-5,7H;1,3-4H2,2H3;;/q;;+1;/p-1/fC6H5S.C4H9.Cu.Li/h7h;;;/q-1;;m;/rC10H14CuLiS/c1-2-3-9-11(12)13-10-7-5-4-6-8-10/h4-8H,2-3,9H2,1H3

InChIKey = HRSUSAKFJNOOQD-SAMBODJZCJ

(primary heterocuprate capable of nucleophilic additions and substitutions[2])

Solubility: sol THF, ether.

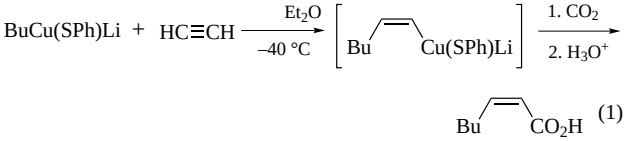
Analysis of Reagent Purity: an assay to determine relative thermal stabilities[3] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl, and the yield of PhCO(*n*-Bu) is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: 1.0 equiv of butyllithium is added dropwise to a 0.2 M, 0 °C THF solution of thiophenol in a three-neck flask equipped with N_2 inlet, solid addition funnel, and rubber septum; after stirring for 10 min, 1.0 equiv of copper(I) iodide is added via the addition funnel; stirring for an additional 15 min provides a clear, yellow solution which is cooled to −78 °C; 1.0 equiv of *n*-BuLi is then added dropwise via syringe;[4,5] after 1 h, the light brown, opaque solution is ready for use. Alternate sources of PhSCu may be acceptable; PhSCu in purities of 95–>98% is commercially available.[6]

Handling, Storage, and Precautions: use in a fume hood; best results are obtained with high-purity copper(I) salts,[7] dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides;[8] *n*-BuLi is pyrophoric,[9] and due care must be exercised in its handling; the reagent has greater stability in THF than in ether; thermal decomposition is minimal at or below −25 °C but is substantial at 0 °C.[3b]

This primary alkyl organometal reagent is representative of the heterocuprate class of organocopper reagents.[10] The *n*-Bu group is nucleophilically reactive, whereas the SPh group is not. Such nontransferable groups are called dummy ligands;[11] the SPh dummy ligand in particular provides enhanced thermal stability and solubility compared with the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when relatively high reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Lithium *n*-butyl(phenylthio)cuprate has been used in nucleophilic substitution reactions of arenesulfonyl fluorides,[12] allylic acetates,[13] 9-BBN,[14] propargylic carbamates,[15] and bromoalkenes,[16] as well as in nucleophilic additions to acetoxyepoxides.[17] It is a good choice for 1,4-addition of an *n*-Bu group, having been used in 1,4-addition–elimination reactions of α-oxoketene dithioacetals[4] and 3-halo-2-cycloalkenones,[18] and in tandem vicinal dialkylation reactions of 5-methyleneoxazolones[19] and alkynes.[20] A typical example is the use of the reagent in the stereospecific synthesis of (*Z*)-2-heptenoic acid from acetylene (eq 1).[20a]



Related Reagents. For related heterocuprates, see lithium methyl(phenylthio)cuprate; for discussion of lithium dialkylcuprates, see lithium dimethylcuprate.

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1. (a) Lipshutz, B. H.; Sengupta, S., *Org. React.* **1992**, *41*, 135. (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

2. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992. (b) Kozlowski, J. A., *Comprehensive Organic Synthesis* **1991**, *4*, 169. (c) Hulce, M.; Chapdelaine, M. J., *Comprehensive Organic Synthesis* **1991**, *4*, 237. (d) Chapdelaine, M. J.; Hulce, M., *Org. React.* **1990**, *38*, 225. (e) Posner, G. H., *Org. React.* **1975**, *22*, 253. (f) Posner, G. H., *Org. React.* **1972**, *19*, 1.
3. (a) Bertz, S. H.; Dabbagh, G., *J. Chem. Soc., Chem. Commun.*, **1982**, 1030. (b) Bertz, S. H.; Dabbagh, G.; Villacorta, G. M., *J. Am. Chem. Soc.* **1982**, *104*, 5824.
4. Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. R.; Kastner, M. E., *J. Am. Chem. Soc.* **1985**, *107*, 4679.
5. (a) Posner, G. H.; Brunelle, D. J.; Sinoway, L., *Synthesis* **1974**, 662. (b) For a detailed preparation of the corresponding *t*-Bu heterocuprate, see Posner, G. H.; Whitten, C. E., *Org. Synth., Coll. Vol.* **1988**, *6*, 248.
6. Corey, E. J.; Boger, D. L., *Tetrahedron Lett.* **1978**, *39*, 4597.
7. Purification methods: (a) Posner, G. H.; Sterling, J. J., *J. Am. Chem. Soc.* **1973**, *95*, 3076. (b) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed; Pergamon: New York, 1988; p 322. (c) Lipshutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M., *Tetrahedron Lett.* **1986**, *27*, 4273.
8. Corey, E. J.; Naef, R.; Hannon, F. J., *J. Am. Chem. Soc.* **1986**, *108*, 7114.
9. Wakefield, B. J. *Organolithium Methods*; Academic: New York, 1988; p 11.
10. Posner, G. H.; Whitten, C. E.; Sterling, J. J., *J. Am. Chem. Soc.* **1973**, *95*, 7788.
11. Lipshutz, B. H., *Synlett* **1990**, 119.
12. Frye, L. L.; Sullivan, E. L.; Cusack, K. P.; Funaro, J. M., *J. Org. Chem.* **1992**, *57*, 697.
13. Kal'yan, Yu. B.; Krimer, M. Z.; Smit, V. A.; Moiseenkov, A. M.; Lutsenko, A. I., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 2092 (*Chem. Abstr.* **1986**, *105*, 97 193n).
14. Whiteley, C. G.; Zwane, I., *J. Org. Chem.* **1985**, *50*, 1969.
15. Pirkle, W. H.; Boeder, C. W., *J. Org. Chem.* **1978**, *43*, 1950.
16. Miller, R. B.; McGarvey, G., *J. Org. Chem.* **1979**, *44*, 4623.
17. Amos, R. A.; Katzenellenbogen, J. A., *J. Org. Chem.* **1977**, *42*, 2537.
18. (a) Piers, E.; Cheng, K. F.; Nagakura, I., *Can. J. Chem.* **1982**, *60*, 1256. (b) Christie, R. M.; Gill, M.; Rickards, R. W., *J. Chem. Soc., Perkin Trans. 1* **1981**, 593.
19. Schulz, G.; Gruber, P.; Steglich, W., *Chem. Ber.* **1979**, *119*, 3221.
20. (a) Alexakis, A.; Normant, J.; Villiéras, J., *Tetrahedron Lett.* **1976**, 3461. (b) Furber, M.; Taylor, R. J. K.; Burford, S. C., *Tetrahedron Lett.* **1985**, *26*, 2731.

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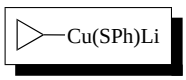
Lithium Cyclopropyl(phenylthio)cuprate[1]



[84180-46-1] $C_9H_{10}CuLiS$ (MW 220.72)

InChI = 1/C6H6S.C3H5.Cu.Li/c7-6-4-2-1-3-5-6;1-2-3-1;;/h1-5,7H;1H,2-3H2;;/q;;;+1/p-1/fC6H5S.C3H5.Cu.Li/h7h;;;/q-1;;;m/rC9H10CuS.Li/c1-2-4-9(5-3-1)11-10-8-6-7-8;/h1-5,8H,6-7H2;/q-1;+1

InChIKey = DORMTGRVQPTVPE-ATQJTTLRCQ

(heterocuprate useful in 1,4-addition–elimination reactions[2] and annulations[3])

Solubility: sol THF; less sol ether.

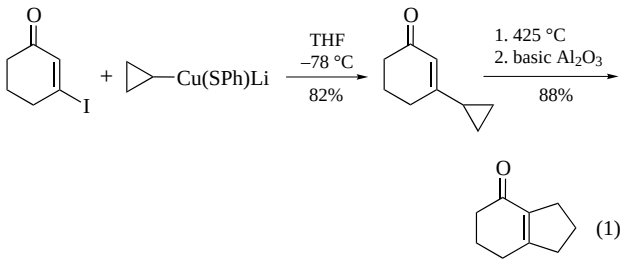
Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl, and the yield of cyclopropyl phenyl ketone is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: cyclopropyllithium[5,6] is prepared by cooling a 0.25 M THF solution of bromocyclopropane under Ar to −78 °C; dropwise addition of 1.0 equiv of a solution of *sec*-butyllithium is followed by stirring for 2 h; this cyclopropyllithium solution is transferred by cannula to a stirred, −78 °C THF slurry of phenylthiocopper(I)[7] under Ar; the resultant mixture is warmed to −20 °C; a clear, light brown solution of cuprate forms after stirring for 20 min; it is cooled to −78 °C and is used directly.[8]

Handling, Storage, and Precautions: best results are obtained with PhSCu prepared from high purity Cu^I salts,[9] dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides;[10] *s*-BuLi is pyrophoric;[11] care must be exercised in its handling, and a fume hood should be used; the reagent is more stable than lithium dicyclopropylcuprate, which decomposes upon prolonged standing at −78 °C.[5]

This cyclopropyl organometal reagent is representative of the heterocuprate class of organocopper reagents.[12] The cyclopropyl group is nucleophilically reactive, whereas the SPh group is not. The nontransferable SPh group, or 'dummy ligand',[13] provides enhanced thermal stability and solubility compared with the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when higher reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Lithium cyclopropyl(phenylthio)cuprate has been used in 1,4-addition– elimination reactions with α-oxoketene dithioacetals[14] and 3-halo-2-alkenones.[8,15] The latter substrates yield 3-cyclopropyl-2-alkenones which undergo high-yield thermal ring expansions, providing a two-step, five-membered ring annulation method.[8] Bicyclo[4.3.0]-1-nonen-2-ones (eq 1) and bicyclo[3.3.0]-1-octen-2-ones of use in the synthesis of zizaene-type sesquiterpenoids can be prepared.[8] Spiro[4.5]-1-decen-6-ones and spiro[4.4]-1-nonen-6-ones, which provide access to vetivane-type sesquiterpenoids, also can be prepared.[15]



(1)

Related Reagents. For related heterocuprates, see lithium methyl(phenylthio)cuprate for discussion of lithium dialkylcuprates, see lithium dimethylcuprate.

1. (a) Lipshutz, B. H.; Sengupta, S., *Org. React.* **1992**, *41*, 135. (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.
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3. Piers, E.; Morton, H. E.; Nagakura, I.; Thies, R. W., *Can. J. Chem.* **1983**, *61*, 1226.
4. Bertz, S. H.; Dabbagh, G., *J. Chem. Soc., Chem. Commun.* **1982**, 1030.
5. Marino, J. P.; Browne, L. J., *J. Org. Chem.* **1976**, *41*, 3629.
6. Alternative preparations include Br–Li exchange in ether[5] using *t*-BuLi and direct lithiation: (a) Seyferth, D.; Cohen, H. M., *J. Organomet. Chem.* **1963**, *1*, 15. (b) Gilman, H.; Cartledge, F. K., *J. Organomet. Chem.* **1964**, *2*, 447.
7. PhSCu in purities of 95–>98% is commercially available. For preparation of PhSCu in THF, see Corey, E. J.; Boger, D. L., *Tetrahedron Lett.* **1978**, *39*, 4597.
8. Piers, E.; Banville, J.; Lau, C. K.; Nagakura, I., *Can. J. Chem.* **1982**, *60*, 2965.
9. Purification methods: (a) Posner, G. H.; Sterling, J. J., *J. Am. Chem. Soc.* **1973**, *95*, 3076. (b) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: New York, 1988; p 322. (c) Lipshutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M., *Tetrahedron Lett.* **1986**, *27*, 4273.
10. Corey, E. J.; Naef, R.; Hannon, F. J., *J. Am. Chem. Soc.* **1986**, *108*, 7114.
11. Wakefield, B. J. *Organolithium Methods*; Academic: New York, 1988; p 11.
12. Posner, G. H.; Whitten, C. E.; Sterling, J. J., *J. Am. Chem. Soc.* **1973**, *95*, 7788.
13. Lipshutz, B. H., *Synlett* **1990**, 119.
14. Dieter, R. K.; Silks, L. A. III; Fishpaugh, J. R.; Kastner, M. E., *J. Am. Chem. Soc.* **1985**, *107*, 4679.
15. Piers, E.; Lau, C. K.; Nagakura, I., *Can. J. Chem.* **1983**, *61*, 288.

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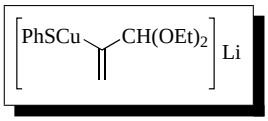
Lithium (3,3-Diethoxy-1-propen-2-yl)-(phenylthio)cuprate[1]



[57428-24-7] $C_{13}H_{18}CuLiO_2S$ (MW 308.87)

InChI = 1/C7H13O2.C6H6S.Cu.Li/c1-4-7(8-5-2)9-6-3;7-6-4-2-1-3-5-6;;/h7H,1,5-6H2,2-3H3;1-5,7H;;/q;;;+1/p-1/fC7H13O2.C6H5S.Cu.Li/h;7h;;/q;-1;;m/rC13H18CuO2S.Li/c1-4-15-13(16-5-2)11(3)14-17-12-9-7-6-8-10-12;/h6-10,13H,3-5H2,1-2H3;/q-1;+1

InChIKey = DIBNJAGQTUHNKQ-KEIHOMMVCK

(α-bromoacrolein-derived heterocuprate capable of nucleophilic additions and substitutions;[2] useful in the preparation of α-methylene-γ-butyrolactones[3])

Alternate Name: lithium [(α-diethoxymethyl)vinyl](phenylthio) cuprate.

Solubility: prepared as a solution in ether; presumably can also be prepared in THF.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl. The yield of phenyl ketone is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: preparation of the heterocuprate[5] requires synthesis of 2-bromo-3,3-diethoxypropene,[6] which can be obtained from the widely available diethyl acetal of acrolein via bromination–dehydrobromination. Under an inert atmosphere of nitrogen or argon, a 0 °C solution of distilled thiophenol in anhydrous ether is treated with 1 equiv of butyllithium. The resultant solution is transferred to a room-temperature suspension of 1 equiv of copper(I) iodide in anhydrous ether under nitrogen or argon, to provide a yellow suspension of phenylthiocopper(I); this suspension is cooled to −78 °C. In a separate flask under nitrogen or argon at −78 °C, 1 equiv of 2-bromo-3,3-diethoxypropene in anhydrous ether is treated dropwise with 1 equiv of *n*-BuLi; the 3,3-diethoxy-2-lithiopropene[7] that results is added dropwise to the −78 °C solution of PhSCu. The heterocuprate that forms is typically reacted with electrophiles at −78 °C with subsequent warming to −40 °C. Modifications using other sources of PhSCu may be acceptable.[8]

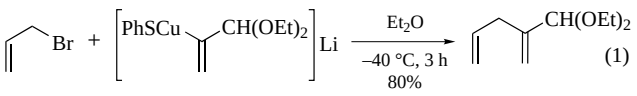
Handling, Storage, and Precautions: best results are obtained with high purity copper(I) salts,[9] dry, oxygen-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides.[10] *n*-BuLi is used to prepare the intermediate reagents lithium thiophenoxide and 3,3-diethoxy-2-lithiopropene, and is pyrophoric;[11] due care must be exercised in its handling. Thermal decomposition occurs at ≥−40 °C. Use in a fume hood.

Introduction. This vinylic organometallic reagent is representative of the heterocuprate class of organocopper reagents.

The vinylic group is reactive as a nucleophile, whereas the SPh group is not. Such nontransferable groups are called dummy ligands;[12] the SPh dummy ligand in particular is typically found to provide enhanced thermal stability and solubility compared to the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when relatively high reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Lithium (3,3-diethoxy-1-propen-2-yl)(phenylthio)cuprate can be used to prepare a variety of 2-substituted propenoic acid derivatives, especially α-methylenelactones. The reagent, along with cognate mixed homocuprate reagents, is generally considered to be superior to analogous (ethoxycarbonyl)vinylcuprate reagents. These latter reagents usually undergo 1,2- as opposed to expected 1,4-additions to α,β-unsaturated carbonyl compounds.[13]

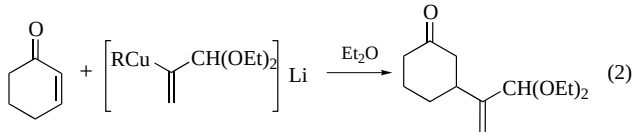
Nucleophilic Substitutions of Halides. Although unreactive with benzyl bromide and vinyl iodides, lithium (3,3-diethoxy-1-propen-2-yl)(phenylthio)cuprate undergoes clean substitutions with allylic bromides[5] to afford 1,4-dienes (eq 1). The mixed homocuprate lithium (3,3-diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate provides similar results.[14]



(1)

1,4-Additions to 2-Alkenones. The reagent undergoes 1,4-addition to cyclohexenone, cyclopentenone, and 3-penten-2-one in 50–80% chemical yields in diethyl ether; the use of THF greatly diminishes formation of 1,4-adducts.[5] A comparative study indicates that mixed homocuprates, especially lithium (3,3-diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate, are the reagents of choice in 1,4-additions (eq 2).[14]

1,4-Adduct (**1**) has been used to prepare α-methylene-δ-valerolactones (eq 3),[5] common structural motifs in marine cembranolides.[3a] If a 4-trimethylsilyloxy- or 4-*t*-butyldimethylsilyloxy-2-cycloalkenone is used as substrate for the 1,4-addition, *trans*-α-methylene-γ-butyrolactones can be prepared;[14] this strategy utilizes the steric control effect of the 4-silyloxy substituent, which causes the nucleophile to attack at the opposing face of the double bond.

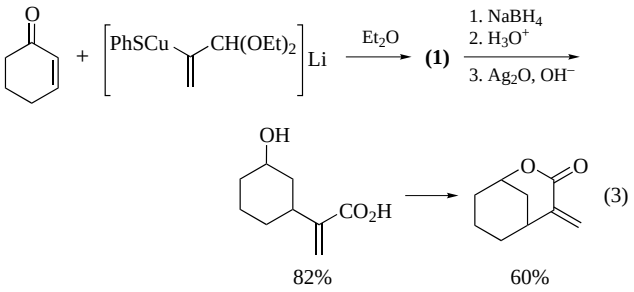


(2)

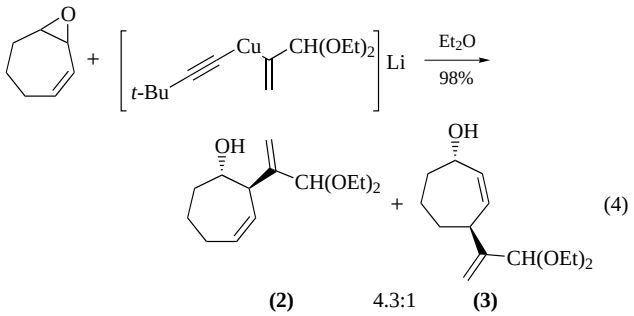
(1)

R = SPh	50%
R = Pr—≡	65%
R = *t*-Bu—≡	92%

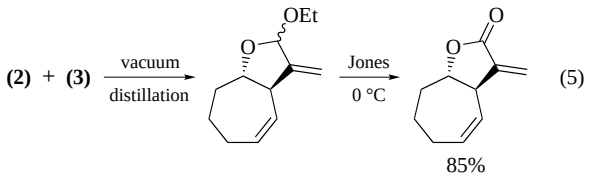
Additions to Epoxides. Although the phenylthiocuprate is reported to be unreactive with cyclohexene epoxide, the homocuprate lithium bis(3,3-diethoxy-1-propen-2-yl)cuprate and mixed homocuprate lithium (3,3-diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate undergo both 1,2- and 1,4-additions to cycloalkadiene monoepoxides (eq 4).[15] 1,4-Addition is distinctly favored when diethyl ether is used as solvent. The hydroxyacetal adducts can be used in the stereospecific construction of α-methylene-γ-butyrolactones of 1,3-diols. For example, when (**2**) is isolated from (**3**) by vacuum distillation, transacetalization affords a cyclic mixed acetal. Upon oxidation with Jones reagent, the corresponding *trans*-α-methylene-γ-butyrolactone is isolated (eq 5). If 1,4-adduct (**3**) is hydrolyzed, the resultant aldehyde can be oxidized to its corresponding acid; iodolactonization provides a *cis*-α-methylene-γ-butyrolactone (eq 6).



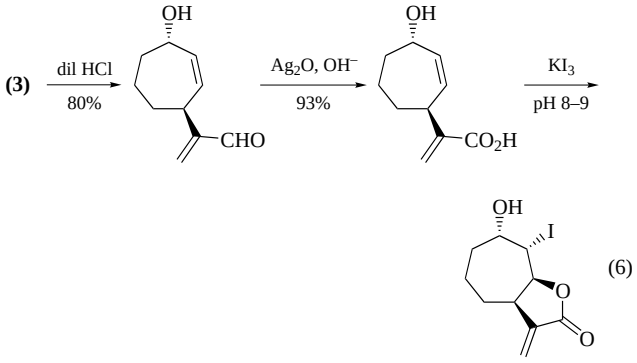
(3)



(4)



(5)



(6)

Other potential methods to prepare 2-substituted propenoic acid derivatives include Pd-catalyzed formylation of vinyl iodides and

vinyl triflates.[16] and hydrocupration of alkyl propiolates using hexa-μ-hydrohexakis(triphenylphosphine)hexacopper.[17]

Related Reagents. 3, 3-Diethoxy-1-propen-2-ylcopper; Lithium Bis(3,3-diethoxy-1-propen-2-yl)cuprate; and Lithium (3,3-Diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate; for related heterocuprates, see Lithium Methyl(phenylthio)-cuprate; for discussion of lithium dialkylcuprates, see Lithium Dimethyl cuprate.

1. (a) Lipshutz, B. H.; Sengupta, S., *Org. React.* **1992**, *41*, 135. (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.
2. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992. (b) Kozlowski, J. A., *Comprehensive Organic Synthesis* **1991**, *4*, 169. (c) Hulce, M.; Chapdelaine, M. J., *Comprehensive Organic Synthesis* **1991**, *4*, 237. (d) Chapdelaine, M. J.; Hulce, M., *Org. React.* **1990**, *38*, 225. (e) Posner, G. H., *Org. React.* **1975**, *22*, 253. (f) Posner, G. H., *Org. React.* **1972**, *19*, 1.
3. For a recent review: Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J., *Synthesis* **1986**, 157. As components in total syntheses of natural products:(a) Marshall, J. A. In *Studies in Natural Products Chemistry*; Rahman, A.-U., Ed.; Elsevier: New York, 1992; Vol. 10, p 3. (b) McMurray, J. E. Dushin, R. G. In *Studies in Natural Products Chemistry*; Rahman, A.-U., Ed.; Elsevier: New York, 1991; Vol. 8, p 15.
4. Bertz, S. H.; Dabbagh, G., *J. Chem. Soc., Chem. Common.* **1982**, 1030.
5. Grieco, P. A.; Wang, C.-L. W.; Majetich, G., *J. Org. Chem.* **1976**, *41*, 726.
6. Claisen, L., *Chem. Ber.* **1898**, *31*, 1015.
7. Ficini, J.; Depezay, J.-C., *Tetrahedron Lett.* **1969**, 4797.
8. (a) For preparation of PhSCu in THF, see Corey, E. J.; Boger, D. L., *Tetrahedron Lett.* **1978**, 4597. (b) PhSCu in purities of 95–>98% is commercially available.
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10. Corey, E. J.; Naef, R.; Hannon, F. J., *J. Am. Chem. Soc.* **1986**, *108*, 7114.
11. Wakefield, B. J. *Organolithium Methods*; Academic: New York, 1988; p 11.
12. Lipshutz, B. H., *Synlett* **1990**, 119.
13. Marino, J. P.; Floyd, D. M., *Tetrahedron Lett.* **1975**, 3897.
14. Boeckman, R. K. Jr.; Ramaiah, M., *J. Org. Chem.* **1977**, *42*, 1581.
15. Marino, J. P.; Farina, J. S., *J. Org. Chem.* **1976**, *41*, 3213.
16. (a) Baillargeon, V. P.; Stille, J. K., *J. Am. Chem. Soc.* **1986**, *108*, 452. (b) Schoenberg, A.; Heck, R. F., *J. Am. Chem. Soc.* **1974**, *96*, 7761.
17. Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M., *J. Am. Chem. Soc.* **1988**, *110*, 291.

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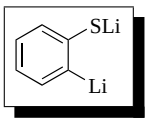
Lithium 2-Lithiobenzenethiolate



[117526-82-6] $C_6H_4SLi_2$ (MW 122.05)

InChI = 1/C6H5S.2Li/c7-6-4-2-1-3-5-6;;/h1-4,7H;;/q;;+1/p-1/fC6H4S.2Li/h7h;;/q-1;;m/rC6H4Li2S/c7-5-3-1-2-4-6(5)9-8/h1-4H

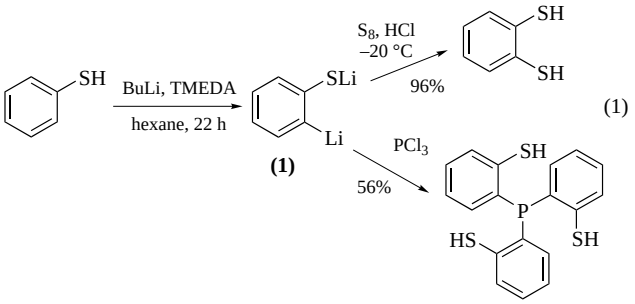
InChIKey = APWYCTQUEYBITB-YKPVEEGCCU

(reagent for preparation of *ortho*-substituted thiophenols[1])

Preparative Methods: easily prepared in the form of a white viscous slurry by stirring thiophenol with 2 equiv butyllithium and 2 equiv *N,N,N′,N′*-tetramethylethylenediamine in dry cyclohexane in a nitrogen atmosphere for 20 h.[1] No purification of the crude product is generally required. It is stable in the absence of air and moisture.

Handling, Storage, and Precautions: the title reagent (**1**) is best made as needed and should be handled and stored under nitrogen in a fume hood. Both preparation and decomposition of (**1**) on exposure to moisture release the foul smelling, toxic thiophenol. Great care should be taken in disposing of (**1**) and cleaning apparatus exposed to (**1**). Excess thiophenol or reagent (**1**) should be destroyed in a good fume hood using an oxidizing agent such as sodium hypochlorite solution.

Reaction with Electrophiles. Diverse thiophenols can be prepared by trapping 2-LiC_6H_4SLi (**1**) with various electrophiles, as illustrated in eq 1 and Table 1.

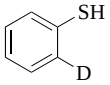
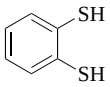
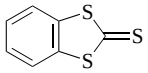
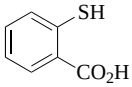
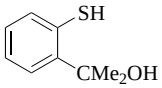
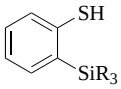
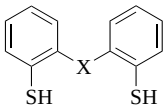
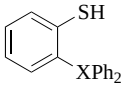
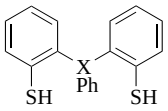
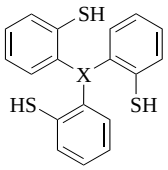
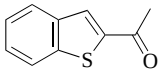


(1)

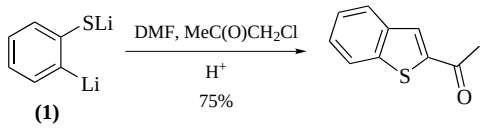
If 2-LiC_6H_4SLi is treated with elemental sulfur[1b] followed by acid,[5] 1,2-benzenedithiol is formed in 96% yield. 1,2,3-Benzenetrithiol can be prepared in 35% yield by extension of this procedure.[1b] This reaction represents the method of choice to prepare 1,2-benzenedithiol. If 2-LiC_6H_4SLi is coupled with chlorophosphines or phosphonic chlorides, a variety of 2-phosphino- or 2-phosphinylbenzenethiols results.[6] These two classes of compounds have utility as multidentate ligands for metals such as Ni,[7a] Os,[7b] and Tc[7c] and have been used in the synthesis of a cyclophane phosphine.[7] With chlorotrimethylsilane, chlorotriethylsilane, chlorotriphenylsilane, and chloro(*t*-butyl)dimethylsilane, the products were the corresponding 2-[tris(organosilyl)]benzenethiols in 92, 79, 43, and 28% yields, respectively.[1b] Multiple silylation could be used to prepare 2,6-bis(trimethylsilyl)benzenethiol in 55% overall yield from

2-LiC_6H_4SLi. With dichlorosilanes or dichlorodisilanes, various bis(thiophenols) could be prepared.[1b] These thiophenols are useful as hindered ligands.[2,3] Through reaction of 2-LiC_6H_4SLi with trichlorosilane, a novel cyclophane silane was prepared.[4]

Table 1 Thiophenols formed by reaction of lithium 2-lithiobenzenethiolate with electrophiles

Electrophile	Product		Yield (%)	Ref.
D_2O			97	1a
S_8			96	1b
$[i\text{-}Pr_2NC(S)S]_2$			67	1c
CO_2			61	1a
Me_2CO			61	1a
R_3SiCl		R = Me R = Et R = Ph R = *t*-$BuMe_2$	92 79 43 28	1b, c
Me_2SiCl_2		X = $SiMe_2$ X = $[SiMe_2]_2$ X = $[SiMe_2\text{-}CH_2]_2$	44 40 33	1b
Ph_2XCl		X = P X = P=O	65 67	6
$PhXCl_2$		X = P X = P=O	76 63	6
XCl_3		X = P X = P=O X = SiH	56 67 11	6, 4
DMF, $MeCOCH_2Cl$			75	9

This procedure can be used with substituted thiophenols,[1b] with 2-naphthalenethiol,[1b] and with 2-mercaptopyridine.[8] 2-Acetylbenzo[*b*]thiophene, a key intermediate in the synthesis of the 5-lipoxygenase inhibitor zileuton, has been prepared in 75% overall yield from thiophenol via condensation of lithium 2-lithiobenzenethiolate with DMF followed by chloroacetone (eq 2).[9] If 0.5 equiv of iodine is used instead of chloroacetone, the product is 2,2′-dithiobisbenzaldehyde, a stable precursor to 2-mercaptobenzaldehyde.[9]



(2)

1. (a) Figuly, G. D.; Loop, C. K.; Martin, J. C., *J. Am. Chem. Soc.* **1989**, *111*, 654. (b) Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J., *J. Am. Chem. Soc.* **1989**, *111*, 658. (c) Smith, K.; Lindsay, C. M.; Pritchard, G. J., *J. Am. Chem. Soc.* **1989**, *111*, 665.
2. (a) Block, E.; Kang, H.; Ofori-Okai, G.; Zubieta, J., *Inorg. Chim. Acta* **1989**, *156*, 27. (b) Block, E.; Kang, H.; Ofori-Okai, G.; Zubieta, J., *Inorg. Chim. Acta* **1990**, *167*, 147.
3. (a) Block, E.; Gernon, M.; Kang, H.; Ofori-Okai, G.; Zubieta, J., *Inorg. Chem.* **1989**, *28*, 1263. (b) Block, E.; Brito, M.; Gernon, M.; McGowty, D.; Kang, H.; Zubieta, J., *Inorg. Chem.* **1990**, *29*, 3172.
4. L'Esperance, R. P.; West, A. P., Jr.; Van Engen, D.; Pascal, R. A., Jr., *J. Am. Chem. Soc.* **1991**, *113*, 2672.
5. Giolando, D. M.; Kirschbaum, K., *Synthesis* **1992**, 451.
6. Block, E.; Ofori-Okai, G.; Zubieta, J., *J. Am. Chem. Soc.* **1989**, *111*, 2327.
7. (a) Franolic, J. D.; Wang, W. Y.; Millar, M., *J. Am. Chem. Soc.* **1992**, *114*, 6587. (b) Dilworth, J. R.; Zheng, Y.; Miller, J. R., *J. Chem. Soc., Dalton Trans.* **1992**, 1757. (c) de Vries, N.; Cook, J.; Jones, A. G.; Davison, A., *Inorg. Chem.* **1991**, *30*, 2662.
8. Block, E.; Gernon, M.; Kang, H.; Zubieta, J., *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1342.
9. Basha, A.; Brooks, D. W., *J. Org. Chem.* **1993**, *58*, 1293.

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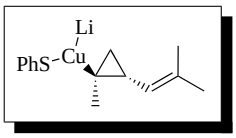
Lithium 1-Methyl-2-(2-methyl-1-(*E*)-propenyl)cyclopropyl(phenylthio)-cuprate



(*E*)
[87084-08-0] $C_{14}H_{18}CuLiS$ (MW 288.88)
InChI = 1/C8H13.C6H6S.Cu.Li/c1-6(2)4-8-5-7(8)3;7-6-4-2-1-3-5-6;;/h4,8H,5H2,1-3H3;1-5,7H;;/q;;+1;/p-1/t8-;;;/s2/f C8H13.C6H5S.Cu.Li/h;7h;;/q;-1;m;/rC14H18CuLiS/c1-11(2)9-12-10-14(12,3)15(16)17-13-7-5-4-6-8-13/h4-9,12H,10H2,1-3H3/t12-,14-/s2
InChIKey = ZUECAIQDKMYAGV-BPYSNLFLDP

(intermediate for the synthesis of natural products, terpenes, and substrates for Cope rearrangement, divinylcyclopropane and [3,3]-sigmatropic shift studies)

Preparative Methods: to a stirred solution of 1.03 g (5.4 mmol) of 1-bromo-1-methyl-2-(2-methyl-1-propenyl)cyclopropane in

50 mL of dry THF–ether (1:1) at −78 °C under nitrogen was added dropwise a solution of *tert*-butyllithium (10.8 mmol) in pentane. After the pale yellow solution had been stirred at −78 °C for 30 min, 0.93 g (5.4 mmol) of phenylthiocopper(I) was added from a bent tube attached to the reaction flask. The suspension was warmed to −20 °C and stirred for 30 min, which gave a red brown solution of the cuprate. The solution was cooled to −78 °C for addition to the iodo enone.[2]

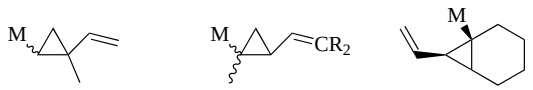
Handling, Storage, and Precautions: best used immediately following its preparation. THF and ether need to be anhydrous (distill from sodium benzophenone). Air and moisture should be excluded.

The title reagent (**4m**) and the related reagents (**1**–**5**) shown in Table 1[2–12] are generally used to prepare divinylcyclopropanes that undergo Cope rearrangements to form seven-membered rings (eq 1). Formation and rearrangement of (**7**) is nearly quantitative, yielding a single product (**8**), which was converted to (±)-*β*-himachalene. In this case, the *trans* cuprate gave excellent results, but in certain other cases a *cis* cuprate is desirable[1,7] (see below).

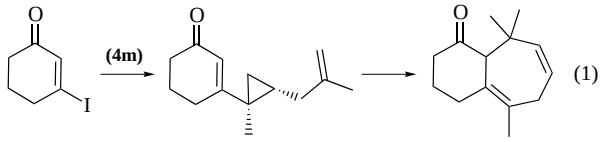
(1h) R = H
(1m) R = Me
(1s) R = SPh

(2)

M = Li, MgBr, PhSCuLi or CuLi (dimer) (see Table 1)



(3) **(4h)** R = H, **(4m)** R = Me **(5)**



(1)

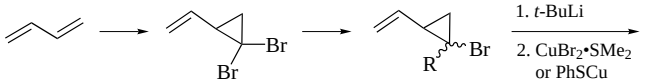
(6) **(7)** **(8)**

Preparation of Vinylcyclopropyl Bromides and their Organolithium Derivatives. The bromides corresponding to reagents (**1h**) and (**4h**) were prepared by adding the dibromocarbene to butadiene and then replacing one bromide (eq 2). Treatment of (**9**) with *t*-butyllithium and then either hydrogen bromide or iodomethane gives mixtures of products with the *trans* isomer predominating.[4,5] (see Table 1 for ratios). The *cis* and *trans* bromides are separable by spinning band distillation. Dibromide reduction with tributylstannane or zinc–acetic acid gives mixtures with the *cis* isomer predominating.[6–9] The reaction of (**10**) with *t*-butyllithium produces (**1h**) and (**4h**) (M = Li) which can then be converted to the cuprate using $CuBr_2.SMe_2$ or PhSCu. Starting with 2-methylbutadiene leads to (**3**) in the same way.[11] The lithium reagent (**3**) (M = Li) was converted to the more selective MgBr variant by treatment with magnesium bromide.

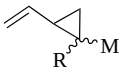
Table 1 Lithium 1-methyl-2-(2-methyl-1-(*E*)-propenyl)cyclopropyl (phenylthio)cuprate and related reagents

Cmpd.	Bromide precursor	Reagent type	*cis*:*trans* or (*Z*):(*E*)[a]	Ref.
(**1h**)	19879-92-6	Li	–	**3**
	15136-02-4 (*trans*)	CuLi	1:4	**4**,**5**
	15136-01-3 (*cis*)	PhSCuLi	7:3, 5:1[b]	**6**–**9**
(**1m**)	64434-67-9 (*E*)	CuLi	1:8[c]	**4**,**5**
(**1s**)		Li	1:4[d]	**4**,**5**
(**2c**)	67885-78-3 (*cis*)	PhSCuLi	20:1	**7**,**10**
(**2t**)	67885-79-4 (*trans*)	PhSCuLi	*trans*	**7**,**10**
(**3**)	60288-35-9 (*Z*)	MgBr	(*Z*)	**11**
(**4h**)	61782-54-5 (*Z*)	CuLi	45:55	**4**
	61782-53-4 (*E*)			
(**4m**)	87084-08-0 (*E*)	PhSCuLi	13:87	**2**
(**5**)	76886-06-1	Li	(*Z*)	**12**

[a] Stereochemistry of cyclopropyl ring (*Z*:*E* refers to **3, 4m**, and **5**).
[b] 7:3 from reduction with *n*-Bu_3SnH, 5:1 from reduction with Zn/ether–HOAc.[6] [c] Double bond stereochemistry 4:1 *cis*/*trans*. [d] Double bond stereochemistry 3:5 *cis*/*trans*.



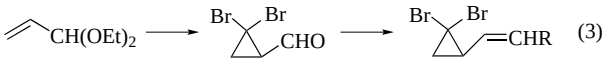
(9) **(10h)** R = H **(10m)** R = Me



(2)

(1h) R = H, M = CuLi (dimer)
(4h) R = Me, M = PhSCuLi

To obtain a substituted vinyl group,[4,5] acrolein acetal (**11**) was converted to the dibromide (**12**), which reacts with ethylidenetriphenylphosphorane or diethyl phenylthiomethylphosphonate to form (**13**) (eq 3). Treatment with *t*-butyllithium followed by HBr formed the monobromide and then reaction with *t*-butyllithium produced (**1m**) or (**1s**).



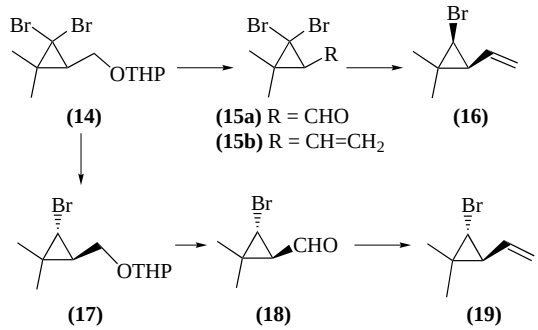
(3)

(11) **(12)** **(13)** R = Me or SPh

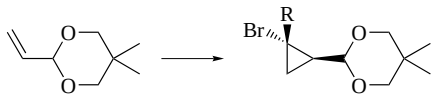
A highly stereoselective synthesis[7] of (**2c**) and (**2t**) starts with dibromocarbene addition to the THP derivative of 3-methyl-2-buten-1-ol to produce (**14**) (eq 4). Hydrolysis of the THP ether, pyridinium chlorochromate oxidation, and Wittig alkenation results in (**15b**), which undergoes Zn/acetic acid reduction to selectively form *cis*-bromide (**16**). Treatment of (**14**) with *n*-BuLi gives only *trans*-bromide (**17**), which was converted to *trans*-bromide (**19**) by hydrolysis, PCC oxidation, and Wittig reaction. Both (**16**) and (**19**) were converted to thiophenylcuprates in the same way as the title compound.

In a similar way (eq 5),[2] acetal (**20**) was transformed into (**21**) which was treated with *n*-BuLi/MeI in HMPA–THF to selectively make (**22**). The mixture (ca. 90% *trans*) could be separated by chromatography and crystallization. Hydrolysis of the acetal in

formic acid followed by Wittig reaction with isopropylidenetriphenylphosphorane generated the bromide needed to produce the *trans* cuprate (**4m**) (M = PhSCuLi).

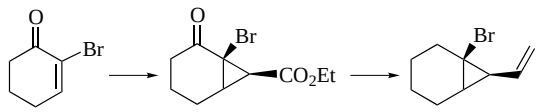


(14) **(15a)** R = CHO **(15b)** R = CH=CH_2 **(16)** **(17)** **(18)** **(19)** (4)



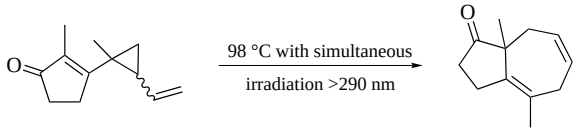
(20) **(21)** R = Br **(22)** R = Me (5)

Bromoenone (**23**) and $Me_2SCH_2CO_2Et$ have been combined[12] to form (**24**) (eq 6), which was elaborated to (**25**) by a five-step sequence. Bromide (**25**) was converted to (**5**) (M = Li) using *t*-butyllithium.



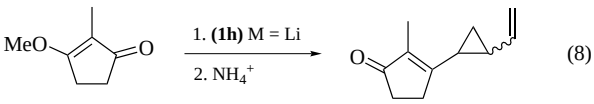
(23) **(24)** **(25)** (6)

Stereochemistry of Divinylcyclopropane Rearrangements. For reagents (**1**)–(**5**), the *cis* isomers lead to the *cis*-divinylcyclopropanes that are excellent substrates for the Cope rearrangement. However, in many cases the *trans*-divinylcyclopropane works sufficiently well that separating *cis* and *trans* isomers is not necessary.[1] In certain compounds where the Cope rearrangement is disfavored by steric factors, *cis* to *trans* isomerization and 1,5-shifts compete with the Cope rearrangement.[7] In one such case (eq 7), an ingenious simultaneous photolysis/thermolysis overcame these side reactions and gave a high yield of Cope product from a *cis*/*trans* mixture.[13]



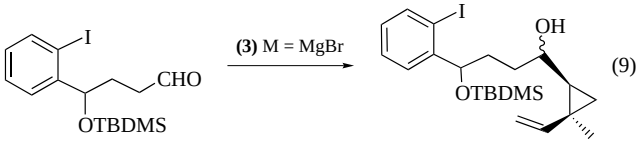
(7)

Choice of Organometallic Reagent. The cuprate reagents (**1**), (**2**), and (**4**) have been used effectively for coupling reactions with β-iodoenones,.[2,7,9,10] e.g. (**6**) or 2-iodomethylenecyclohexanone, acyl chlorides[6,8] (followed by conversion to the silyl enol ether), propargyl ketones,[5] and propargyl esters.[5] The phenylthiocuprates are efficient for transfer of secondary and tertiary cyclopropyl compounds and are readily made from phenylthiocopper(I).[14] The lithium reagents add in 1,2-fashion to β-alkoxy enolates[3–15] to form some of the same compounds available from the cuprate route exemplified in eq 1 For example (eq 8), 3-methoxy-2-methylcyclopentanone gives products similar to (**7**).



(8)

They can also be used to add to aldehydes or ketones (eq 9); the resultant alcohol group can then be used to form the second vinyl group. Scopadulcic acid-B has been prepared[11] using this approach with (**3**) (M = MgBr). The lithium reagent (**3**) (M = Li) was found to attack the aryl iodide of the starting aldehyde. Some of the lithium reagents have also been used to prepare chromium carbene complexes.[16]



(9)

1. (a) Piers, E., *Comprehensive Organic Synthesis* **1991**, *5*, 971. (b) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G., *Org. React.* **1992**, *41*, 1.
2. Piers, E.; Ruediger, E. H., *Can. J. Chem.* **1983**, *61*, 1239.
3. Wender, P. A.; Filosa, M. P., *J. Org. Chem.* **1976**, *41*, 3490.
4. Marino, J. P.; Browne, L. J., *Tetrahedron Lett.* **1976**, 3241.
5. Marino, J. P.; Browne, L. J., *Tetrahedron Lett.* **1976**, 3245.
6. Piers, E.; Burmeister, M. S.; Reissig, H.-U., *Can. J. Chem.* **1986**, *64*, 180.
7. Piers, E.; Morton, H. E.; Nagakura, I.; Thies, R. W., *Can. J. Chem.* **1983**, *61*, 1226.
8. Piers, E.; Reissig, H.-U., *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 791.
9. Piers, E.; Nagakura, I., *Tetrahedron Lett.* **1976**, 3237.
10. Piers, E.; Nagakura, I.; Morton, H. E., *J. Org. Chem.* **1978**, *43*, 3630.
11. Overman, L. E.; Ricca, D. J.; Tran, V. D., *J. Am. Chem. Soc.* **1993**, *115*, 2042.
12. Wender, P. A.; Hillemann, C. L.; Szymonifka, M. J., *Tetrahedron Lett.* **1980**, *21*, 2205.
13. Wender, P. A.; Eissenstat, M. A.; Filosa, M. P., *J. Am. Chem. Soc.* **1979**, *101*, 2196.
14. Posner, G. H.; Brunelle, D. J.; Sinoway, L., *Synthesis* **1974**, 662.
15. Murata, I.; Sugihara, Y.; Sugimura, T.; Wakabayashi, S., *Tetrahedron* **1986**, *42*, 1745.
16. Tumer, S. U.; Herndon, J. W.; McMullen, L. A., *J. Am. Chem. Soc.* **1992**, *114*, 8394.

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Lithium Phenylthio(trimethylstannyl)-cuprate

$Me_3SnCu(SPh)Li$

[69608-62-4] $C_9H_{14}CuLiSSn$ (MW 343.50)

InChI = 1/C6H6S.3CH3.Cu.Li.Sn/c7-6-4-2-1-3-5-6;;;;;;/h1-5,7H;3*1H3;;;/q;;;;+1;;/p-1/fC6H5S.3CH3.Cu.Li.Sn/h7h;;;;;;/q-1;;;;m;;/rC9H14CuLiSSn/c1-13(2,3)10(11)12-9-7-5-4-6-8-9/h4-8H,1-3H3

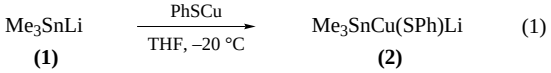
InChIKey = XBDVYQSHGIOFIP-XTONOMFICO

(trimethyltin transfer to the β-carbon of α,β-unsaturated carbonyl compounds[1–5] and α,β-alkynic carboxylic acid derivatives[6–12])

Physical Data: prepared in situ; the THF solution is dark red.

Solubility: sol THF.

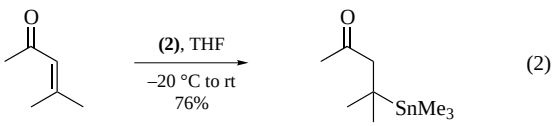
Preparative Methods: lithium (phenylthio)(trimethylstannyl)-cuprate (**2**) is prepared by the addition of solid phenylthiocopper(I)[14] to a THF solution of trimethylstannyllithium (**1**)[15] (eq 1).



(1)

Handling, Storage, and Precautions: should be prepared in dry solvent and used under an inert atmosphere. Since organotin compounds are toxic,[13] reaction workup should be carried out in a fume hood.

Reaction with α,β-Unsaturated Carbonyl Systems. Reagent (**2**) readily effects conjugate addition of the Me_3Sn moiety to a variety of α,β-unsaturated carbonyl compounds, including enones,.[1,2] β-iodo enones,[1,2] and β-trifluoromethanesulfonyl enoates[3] (eqs 2–4). Notably, the intermediate enolate anion derived from the reaction of (**2**) with (*R*)-(−)-5-methyl-2-cyclohexen-1-one can be trapped with iodomethane to give, stereoselectively, the ketone (**3**) (eq 5).[4,16] It is pertinent to mention that the conjugate additions of reagents (**1**) and (**2**) to bicyclic enones are stereochemically complementary. For example, reaction of (**4**) with (**1**) affords the *trans*-fused substance (**5**), while reagent (**2**) converts (**4**) into the *cis*-isomer (**6**).[5,17]



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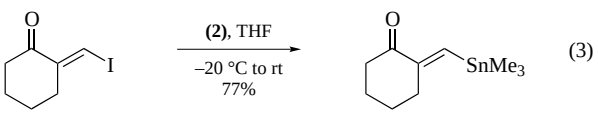
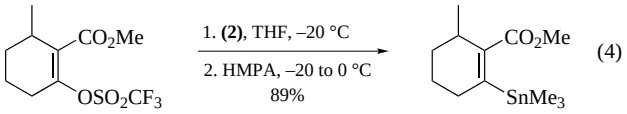


(3)



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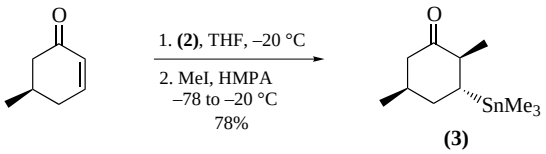

(5)

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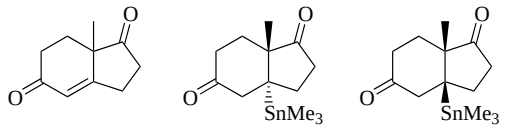
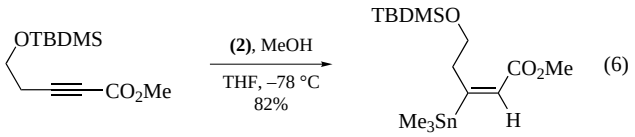
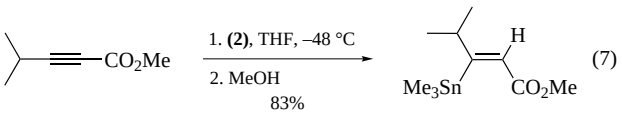


(4) **(5)** **(6)**

Reaction with α,β-Alkynic Carboxylic Acid Derivatives. The stereochemical outcome of the regioselective addition of the elements of Me_3Sn–H across the triple bond of α,β-alkynic esters by reagent (**2**) can be controlled simply by varying the reaction conditions. Thus, reaction at −78 °C in the presence of a proton source provides alkyl (*E*)-3-trimethylstannyl-2-alkenoates (eq 6),[6–8] while use of the reaction conditions outlined in eq 7 produces the corresponding (*Z*)-isomers.[6–18] Similar stereochemical control can be accomplished with α,β-alkynic *N*,*N*-dimethylamides as substrates.[9] Alkyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates have been shown to be useful synthetic intermediates in a range of contexts, including natural product syntheses.[6,8,10,12,16b,19]

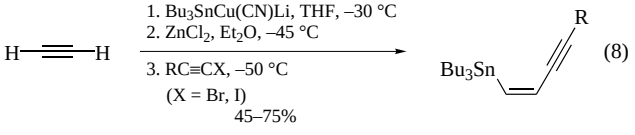


(6)



(7)

Related Reagents. A number of lower order heterocuprates related in composition to (**2**) have been reported. These include $Me_3SnCu(Y)Li$ (Y = C≡CCMe$_2$OMe.[2,7,20] and CN[2,18]) and $Bu_3SnCu(Y)Li$ (Y = SPh[2,21] and CN[22–24]). To date, these reagents have been employed primarily in reactions similar to some of those described above for (**2**) A recent report describing the use of $Bu_3SnCu(CN)Li$ for the preparation of (*Z*)-1-tributylstannyl-1-alken-3-ynes (eq 8)[24] is noteworthy.



(8)

See also 2,3-Bis(trimethylstannyl)-1,3-butadiene; 4-Chloro-2-trimethylstannyl-1-butene; (E)-1-Lithio-2-tributylstannylethylene; Methyl Tributylstannyl Sulfide; trans-1,2-bis(tributylstannyl)ethylene; Tributylstannylacetylene; Tributylstannylcopper; Tributylstannyllithium; Trimethylstannylcopper–dimethyl Sulfide; 2-Trimethylstannylmethyl-1,3-butadiene; Trimethylstannyllithium; and (Triphenylstannylmethyl)lithium.

1. Piers, E.; Morton, H. E., *J. Chem. Soc., Chem. Commun.* **1978**, 1033.
2. Piers, E.; Morton, H. E.; Chong, J. M., *Can. J. Chem.* **1987**, *65*, 78.
3. Piers, E.; Tse, H. L. A., *Tetrahedron Lett.* **1984**, *25*, 3155; *Can. J. Chem.* **1993**, *71*, 983.
4. Piers, E.; Roberge, J. Y., *Tetrahedron Lett.* **1991**, *32*, 5219.
5. Fujiwara, J.; Yamamoto, T.; Sato, T., *Chem. Lett.* **1992**, 1775.
6. Piers, E.; Morton, H. E., *J. Org. Chem.* **1980**, *45*, 4263.
7. Piers, E.; Chong, J. M.; Morton, H. E., *Tetrahedron Lett.* **1981**, *22*, 4905; *Tetrahedron* **1989**, *45*, 363.
8. Piers, E.; Gavai, A. V., *J. Chem. Soc., Chem. Commun.* **1985**, 1241; *J. Org. Chem.* **1990**, *55*, 2374.
9. Piers, E.; Chong, J. M.; Keay, B. A., *Tetrahedron Lett.* **1985**, *26*, 6265.
10. Piers, E.; Friesen, R. W., *J. Org. Chem.* **1986**, *51*, 3405; *Can. J. Chem.* **1992**, *70*, 1204.
11. Piers, E.; Wai, J. S. M., *J. Chem. Soc., Chem. Commun.* **1987**, 1342; *Can. J. Chem.* **1994**, *72*, 146.
12. Piers, E.; Friesen, R. W.; Rettig, S. J., *Can. J. Chem.* **1992**, *70*, 1385.
13. Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987; p 6.
14. Posner, G. H.; Brunelle, D. J.; Sinoway, L., *Synthesis* **1974**, 662.
15. Still, W. C., *J. Am. Chem. Soc.* **1977**, *99*, 4836.
16. The enantiomerically homogeneous substance **3** has been employed as an intermediate for the synthesis of *trans*-clerodane diterpenoids: (a) Ref.4 (b) Piers, E.; Roberge, J. Y., *Tetrahedron Lett.* **1992**, *33*, 6923.
17. See also Plamondon, L.; Wuest, J. D., *J. Org. Chem.* **1991**, *56*, 2066.
18. Similar chemistry can be achieved by use of the lower order cuprate $Me_3SnCu(CN)Li$: Piers, E.; Wong, T.; Ellis, K. A., *Can. J. Chem.* **1992**, *70*, 2058.
19. (a) Piers, E.; Friesen, R. W., *Can. J. Chem.* **1987**, *65*, 1681. (b) Piers, E.; Lu, Y.-F., *J. Org. Chem.* **1988**, *53*, 926. (c) Piers, E.; Llinas-Brunet, M., *J. Org. Chem.* **1989**, *54*, 1483. (d) Piers, E.; Gavai, A. V., *J. Org. Chem.* **1990**, *55*, 2380. (e) Piers, E.; Ellis, K. A., *Tetrahedron Lett.* **1993**, *34*, 1875. (f) Piers, E.; Wong, T., *J. Org. Chem.* **1993**, *58*, 3609.
20. Piers, E.; Chong, J. M., *J. Org. Chem.* **1982**, *47*, 1602.
21. (a) Piers, E.; Chong, J. M.; Gustafson, K.; Andersen, R. J., *Can. J. Chem.* **1984**, *62*, 1. (b) Harris, F. L.; Weiler, L., *Tetrahedron Lett.* **1987**, *28*, 2941. (c) Munt, S. P.; Thomas, E. J., *J. Chem. Soc., Chem. Commun.* **1989**, 480. (d) Lowinger, T. B.; Weiler, L., *Can. J. Chem.* **1990**, *68*, 1636. (e) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Horita, K.; Parkinson, C. J., *J. Chem. Soc., Chem. Commun.* **1992**, 1238.
22. (a) Marino, J. P.; Long, J. K., *J. Am. Chem. Soc.* **1988**, *110*, 7916. (b) Marino, J. P.; Emonds, M. V. M.; Stengel, P. J.; Oliveira, A. R. M.; Simonelli, F.; Ferreira, J. T. B., *Tetrahedron Lett.* **1992**, *33*, 49.
23. Yoneda, R.; Osaki, T.; Harusawa, S.; Kurihara, T., *J. Chem. Soc., Perkin Trans. 1* **1990**, 607.
24. Magriotis, P. A.; Scott, M. E.; Kim, K. D., *Tetrahedron Lett.* **1991**, *32*, 6085.

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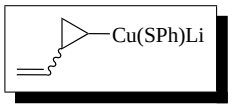
Lithium Phenylthio(2-vinylcyclopropyl)-cuprate[1]



[61754-34-5] $C_{11}H_{12}CuLiS$ (MW 246.79)

InChI = 1/C6H6S.C5H7.Cu.Li/c7-6-4-2-1-3-5-6;1-2-5-3-4-5;;/h1-5,7H;2-3,5H,1,4H2;;/q;;+1;/p-1/fC6H5S.C5H7.Cu.Li/h7h;;;/q-1;;m;/rC11H12CuLiS/c1-2-9-8-11(9)12(13)14-10-6-4-3-5-7-10/h2-7,9,11H,1,8H2

InChIKey = OEDRLCPGDVZUPY-WLYWVZSQCW

(*cis*)

[71647-04-6]

InChI = 1/C6H6S.C5H7.Cu.Li/c7-6-4-2-1-3-5-6;1-2-5-3-4-5;;/h1-5,7H;2-3,5H,1,4H2;;/q;;+1;/p-1/t;5-;;/s2/fC6H5S.C5H7.Cu.Li/h7h;;;/q-1;;m;/rC11H12CuLiS/c1-2-9-8-11(9)12(13)14-10-6-4-3-5-7-10/h2-7,9,11H,1,8H2/t9-,11+/s2

InChIKey = OEDRLCPGDVZUPY-QLXKTPJEDF

(*trans*)

[102511-64-8]

InChI = 1/C6H6S.C5H7.Cu.Li/c7-6-4-2-1-3-5-6;1-2-5-3-4-5;;/h1-5,7H;2-3,5H,1,4H2;;/q;;+1;/p-1/t;5-;;/s2/fC6H5S.C5H7.Cu.Li/h7h;;;/q-1;;m;/rC11H12CuLiS/c1-2-9-8-11(9)12(13)14-10-6-4-3-5-7-10/h2-7,9,11H,1,8H2/t9-,11-/s2

InChIKey = OEDRLCPGDVZUPY-UOHVDULPDH

(heterocuprate useful in 1,4-addition–elimination reactions[2] and annulations[3])

Solubility: sol THF; less sol ether.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl; the yield of 2-vinylcyclopropyl phenyl ketone is measured by GC or HPLC, the response of which is calibrated using authentic product and an appropriate internal standard.

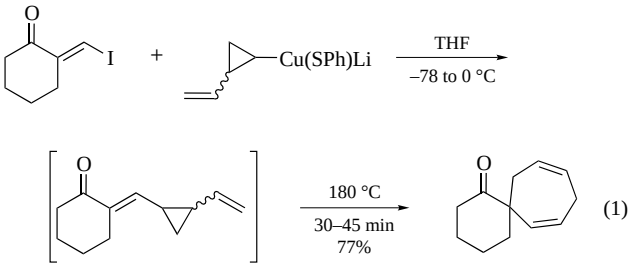
Preparative Method: 2-vinylcyclopropyllithium[5] is prepared by cooling a 0.25 M ether or THF solution of 1-bromo-2-vinylcyclopropane[6] under Ar to −78 °C. Dropwise addition of 1.1–1.4 equiv of a solution of *tert*-butyllithium is followed by stirring for 2 h. One equiv of phenylthiocopper(I)[7] is added, and the resultant slurry is diluted with 5 mL THF per mmol of cyclopropane. The reaction is warmed to −20 °C; a clear, light brown solution of cuprate forms after stirring for 20 min. It is cooled to −78 °C and is used directly.

Handling, Storage, and Precautions: best results are obtained with PhSCu prepared from high purity Cu^I salts,[8] dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides.[9] *t*-BuLi is pyrophoric;[10] care must be exercised in its handling. Use in a fume hood.

This cyclopropyl organometallic reagent is representative of the heterocuprate class of organocopper reagents.[11] Only the cyclopropyl group, and not the SPh group, is nucleophilically reactive. The nontransferable SPh group, or 'dummy ligand',[12]

provides enhanced thermal stability and solubility compared to the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when higher reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Lithium phenylthio(2-vinylcyclopropyl)cuprate has been used in acylations[3] and 1,4-addition–elimination reactions with 3-halo-2-alkenones.[13] The products of these reactions undergo high-yield thermal ring expansions, providing a two-step, seven-membered ring annulation method. 4-Cycloheptenones and various seven-membered ring bicycloalkadienones and spiroalkadienones (eq 1)[13] can be prepared.



(1)

Either the *cis*- or *trans*-isomer or a mixture of isomeric 1-bromo-2-vinylcyclopropanes can be used in the reaction, although rearrangement is more facile with the *cis*-isomer. The method has been used in a convergent total synthesis of the sesquiterpene β-himachalene to assemble the 7,6-fused ring core of the natural product.[14]

Related Reagents. Lithium Bis(2-vinylcyclopropyl)cuprate; Lithium Dimethylcuprate; Lithium Methyl(phenylthio) cuprate.

1. (a) Lipshutz, B. H.; Sengupta, S., *Org. React.* **1992**, *41*, 135. (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.
2. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992. (b) Kozlowski, J. A., *Comprehensive Organic Synthesis* **1991**, *4*, 169. (c) Hulce, M.; Chapdelaine, M. J., *Comprehensive Organic Synthesis* **1991**, *4*, 237. (d) Chapdelaine, M. J.; Hulce, M., *Org. React.* **1990**, *38*, 225. (e) Posner, G. H., *Org. React.* **1975**, *22*, 253. (f) Posner, G. H., *Org. React.* **1972**, *19*, 1.
3. Piers, E.; Burmeister, M. S.; Reissig, H.-U., *Can. J. Chem.* **1986**, *64*, 180.
4. Bertz, S. H.; Dabbagh, G., *J. Chem. Soc., Chem. Commun.* **1982**, 1030.
5. Wender, P. A.; Filosa, M. P., *J. Org. Chem.* **1976**, *21*, 3490.
6. (a) Landgrebe, J. A.; Becker, L. W., *J. Org. Chem.* **1968**, *33*, 1173. (b) Seyferth, D.; Yamazaki, H.; Alleston, D. L., *J. Org. Chem.* **1963**, *28*, 703.
7. PhSCu in purities of 95 to >98% is commercially available. For the preparation of PhSCu in THF, see Corey, E. J.; Boger, D. L., *Tetrahedron Lett.* **1978**, *39*, 4597.
8. Purification methods:(a) Posner, G. H.; Sterling, J. J., *J. Am. Chem. Soc.* **1973**, *95*, 3076. (b) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: New York, 1988; p 322. (c) Lipshutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M., *Tetrahedron Lett.* **1986**, *27*, 4273.
9. Corey, E. J.; Naef, R.; Hannon, F. J., *J. Am. Chem. Soc.* **1986**, *108*, 7114.
10. Wakefield, B. J. *Organolithium Methods*; Academic: New York, 1988; p 11.
11. Posner, G. H.; Whitten, C. E.; Sterling, J. J., *J. Am. Chem. Soc.* **1973**, *95*, 7788.
12. Lipshutz, B. H., *Synlett* **1990**, 119.
13. Piers, E.; Morton, H. E.; Nagakura, I.; Thies, R. W., *Can. J. Chem.* **1983**, *61*, 1226.
14. Piers, E.; Ruediger, E. H., *Can. J. Chem.* **1983**, *61*, 1239.

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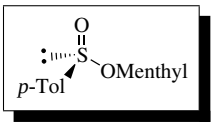
M

(−)-(1*R*,2*S*,5*R*)-Menthyl (*S*)-*p*-Toluenesulfinate



[1517-82-4] $C_{17}H_{26}O_2S$ (MW 294.50)

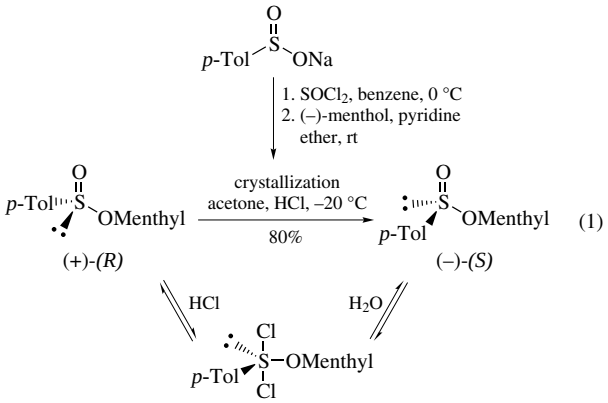
InChI = 1/C17H26O2S/c1-12(2)16-10-7-14(4)11-17(16)19-20(18)15-8-5-13(3)6-9-15/h5-6,8-9,12,14,16-17H,7,10-11H2,1-4H3/t14-,16+,17?,20+/m1/s1

InChIKey = NQICGNSARVCSGJ-KQFYIKDZBE

(agent used for the synthesis of chiral sulfoxides[1,3])

Physical Data: $[\alpha]_D = -202°$ (acetone, $c = 2.0$).

Preparative Method: obtained by reaction of (−)-menthol with *p*-toluenesulfinyl chloride. This esterification showed no particular stereoselectivity, giving an equal amount of the two sulfinate diastereomers.[1] In order to avoid a chromatographic separation, it is possible to epimerize these sulfinate esters in acidic medium and displace the resulting equilibrium towards the less soluble isomer, (−)-menthyl (*S*)-*p*-toluenesulfinate, in 80% yield (eq 1).[2] This procedure was later extended to large scale preparation.[3]

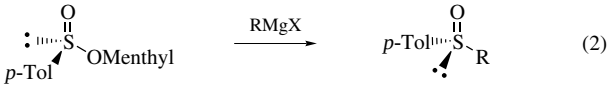


(1)

The absolute configuration of (−)-menthyl (*S*)-*p*-toluenesulfinate was established by correlation with (−)-menthyl *p*-iodobenzenesulfinate, known from X-ray diffraction analysis.[4]

Synthesis of Chiral Sulfoxides.

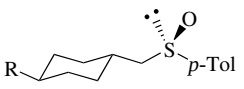
Alkyl Sulfoxides. Any Grignard reagent reacts with (−)-menthyl (*S*)-*p*-toluenesulfinate and displaces the menthoxy group with complete inversion of configuration at sulfur (eq 2; R = Me,[3,5] Et,[5,6] *n*-C_6H_{13}[7]).



(2)

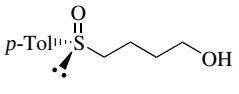
It was also reported that using methyllithium instead of the methyl Grignard could give some racemization of methyl *p*-tolyl sulfoxide as a result of methyl group exchange via a methylene sulfine intermediate.[8]

(*R*)-4-Substituted cyclohexylmethyl *p*-tolyl sulfoxide (**1**)[9] as well as (*R*)-4-hydroxybutyl *p*-tolyl sulfoxide (**2**)[10] and (*R*)-3-butenyl *p*-tolyl sulfoxide (**3**)[11] were also obtained by reaction of (−)-menthyl (*S*)-*p*-toluenesulfinate and the corresponding Grignard reagent.

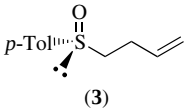


(**1**)

R = Me, $MeOCH_2$, $ClCH_2$

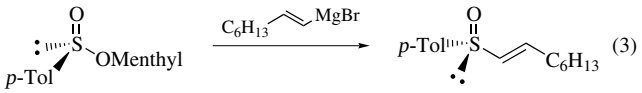


(**2**)



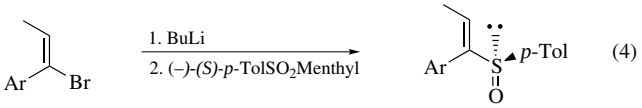
(**3**)

Vinyl Sulfoxides. A stereocontrolled preparation of (*E*)-1-alkenyl *p*-tolyl sulfoxide from (−)-menthyl-(*S*) *p*-toluenesulfinate was reported (eq 3).[12a]



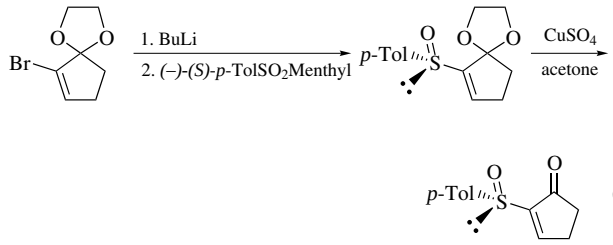
(3)

One example was also reported showing the formation of an (*E*)-alkenyl sulfoxide in the reaction of a vinylic lithium compound on menthyl sulfinate (eq 4).[12b]



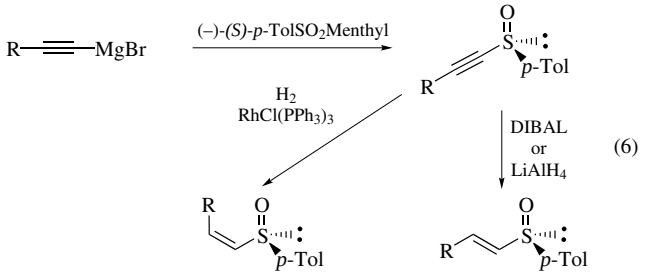
(4)

(+)-(*S*)-2-(*p*-Tolylsulfinyl)-2-cyclopentenone was also prepared by reaction of a vinyllithium derivative and menthyl sulfinate (eq 5).[13]



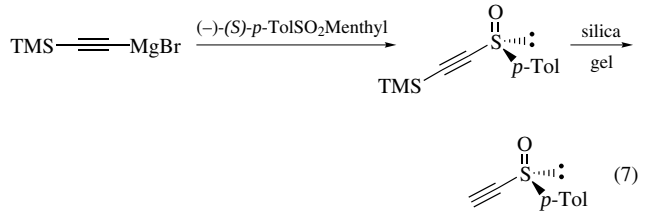
(5)

The preparation of optically pure (*E*)- and (*Z*)-1-alkenyl *p*-tolyl sulfoxides was described via stereoselective reduction of 1-alkynyl *p*-tolyl sulfoxides (eq 6).[14]



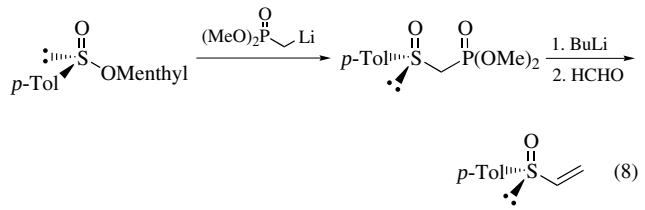
(6)

Alkynic sulfoxides have been made from trimethylsilylethynylmagnesium bromide and the resulting alkyne disilylated on silica gel (eq 7).[15]



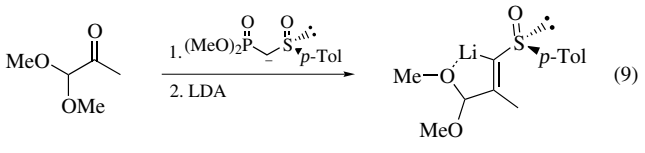
(7)

Chiral vinyl sulfoxides can also be prepared by a Horner–Emmons reaction of carbonyl compounds with α-phosphoryl sulfoxides which are obtained from lithiated dimethyl methylphosphonate and (−)-menthyl (*S*)-*p*-toluenesulfinate (eq 8).[16] However, this reaction applied to carbonyl compounds often gives a mixture of the (*E*) and (*Z*) isomers of the vinylic sulfoxide.



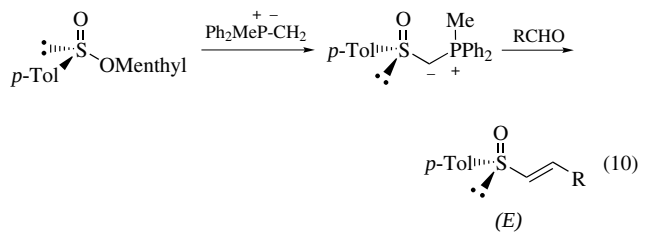
(8)

The reaction of α-phosphoryl sulfoxide with the dimethyl acetal of pyruvic aldehyde allowed the preparation of the corresponding vinylic sulfoxide as a 1:1 mixture of (*E*) and (*Z*) isomers which could be isomerized with lithium diisopropylamide to the lithiated (*E*) isomer, used for the asymmetric synthesis of α-tocopherol (eq 9).[17]



(9)

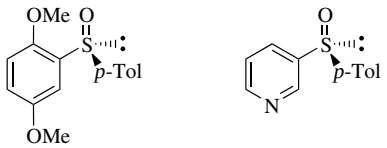
The Wittig reaction of an optically active sulfinylphosphonium ylide was reported to yield only the (*E*)-vinylic sulfoxides (eq 10).[18]



(10)

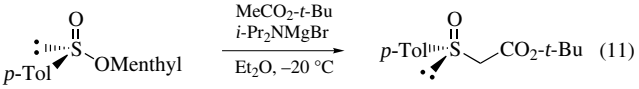
(*E*)

Diaryl Sulfoxides. Optically active diaryl sulfoxides are prepared by reaction of an aryl Grignard with (−)-menthyl (*S*)-*p*-toueneslfinate: 2,5-dimethoxyphenyl *p*-tolyl sulfoxide (**4**), a precursor of sulfinyl quinones,[19] and 3-pyridyl *p*-tolyl sulfoxide (**5**), a precursor of sulfinyl dihydropyridines (studied as NADH model compounds)[20] are two typical examples.



(**4**) (**5**)

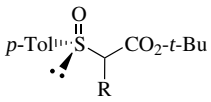
Sulfinyl Esters and Derivatives. (*R*)-(+)-*t*-Butyl 2-(*p*-tolylsulfinyl)acetate is conveniently prepared by reaction of the magnesium enolate of *t*-butyl acetate (readily made with bromomagnesium diisopropylamide) with (−)-menthyl (*S*)-*p*-toluenesulfinate (eq 11).[21]



(11)

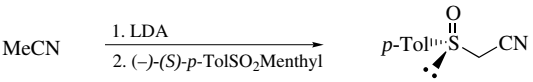
(+)-(*R*)

Substituted sulfinyl esters (**6**) have also been prepared by this reaction using the same base[22a] or lithium cyclohexyl(isopropyl)amide,[22b] which gives higher yields.



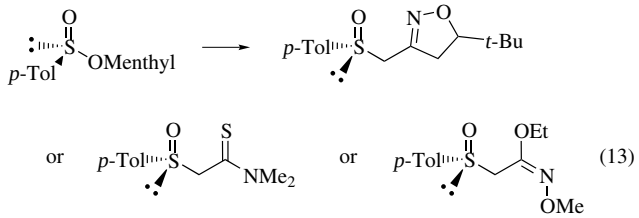
(**6**) R = Me, Et, $C_{14}H_{29}$

The anion of acetonitrile also reacts with (−)-menthyl (*S*)-*p*-toluenesulfinate to give the corresponding β-sulfinylacetonitrile (eq 12).[23]



(12)

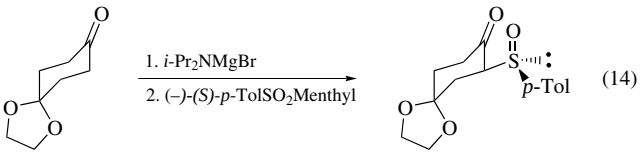
Similarly, *exo*-metalation with LDA of the racemic 3-methyl-4,5-dihydroisoxazole and reaction with (−)-menthyl (*S*)-*p*-toluenesulfinate afforded the sulfinyl-4,5-dihydroisoxazole as a diastereomeric mixture;[24] lithiated *N*,*N*-dimethylthioacetamide leads to the sulfinyl *N*,*N*-dimethylthioacetamide,[25] and lithiated ethyl *N*-methoxyacetimidate leads to *p*-tolylsulfinylethyl-*N*-methoxyacetimidate (eq 13).[26]



(13)

β-Keto Sulfoxides. Cyclic β-keto sulfoxides are readily obtained from the magnesium enolate of the ketone and

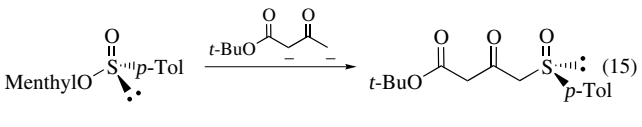
(−)-menthyl (*S*)-*p*-toluenesulfinate[27] as a mixture of diastereomers in which the major epimer has the sulfoxide group in the equatorial orientation (eq 14).



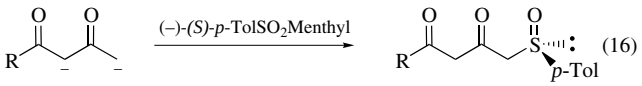
(14)

66% de

By condensation of the dianion of *t*-butyl acetoacetate and (−)-menthyl (*S*)-*p*-toluenesulfinate, the corresponding β-keto sulfoxide was obtained in high yield (eq 15) and shown to be an efficient precursor of both enantiomers of β-hydroxybutyric acid via selective reduction of the ketone carbonyl group.[28] β,δ-Diketo sulfoxides were prepared in a similar way from diketone dianions (eq 16).[29]



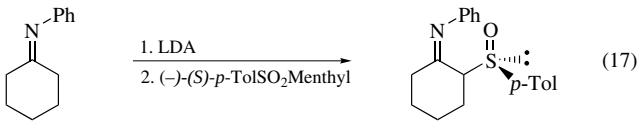
(15)



(16)

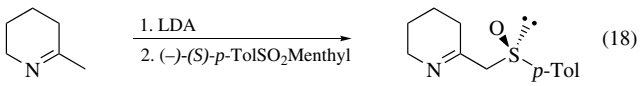
R = Me, Ph

Imino Sulfoxides. Metalated imines reacted with (−)-menthyl (*S*)-*p*-toluenesulfinate to yield the corresponding sulfinylimines as a diastereoisomeric mixture (eq 17).[30]



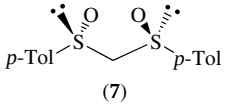
(17)

Similarly, *exo*-metalated cyclic imines afforded the sulfinylimines as an alkaloid precursor (eq 18).[31]

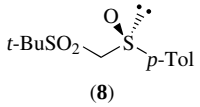


(18)

Miscellaneous. (*S,S*)-Bis(*p*-tolylsulfinyl)methane (**7**) is readily prepared from (−)-menthyl (*S*)-*p*-toluenesulfinate and (*R*)-methyl *p*-tolyl sulfoxide.[32] (+) (*S*)-*p*-Tolylsulfinylmethyl *t*-butyl sulfone (**8**) was made from the *t*-butyl methyl sulfone anion and (−)-menthyl (*S*)-*p*-toluenesulfinate.[33]

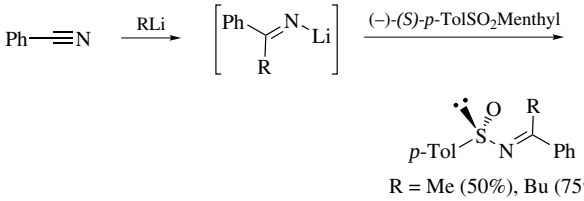


(**7**)



(**8**)

Chiral *N*-benzylidene *p*-toluenesulfinamides were prepared by reaction of benzonitrile with an alkyllithium followed by addition of (−)-menthyl (*S*)-*p*-toluenesulfinate and converted into optically active amines and amino acids (eq 19).[34]



(19)

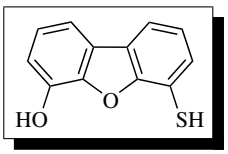
R = Me (50%), Bu (75%)

1. Solladié, G., *Synthesis* **1981**, 185.
2. Mioskowski, C.; Solladié, G., *Tetrahedron* **1980**, *36*, 227.
3. Solladié, G.; Hutt, J.; Girardin, A., *Synthesis* **1987**, 173.
4. Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L., *J. Am. Chem. Soc.* **1965**, *87*, 1958.
5. Andersen, K. K., *J. Org. Chem.* **1964**, *29*, 1953.
6. Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T., *Tetrahedron Lett.* **1985**, *26*, 6205.
7. Bravo, P.; Resnati, G.; Viani, F.; Arnone, A., *Tetrahedron* **1987**, *43*, 4635.
8. Jacobus, J.; Mislow, K., *J. Am. Chem. Soc.* **1967**, *89*, 5228.
9. Solladié, G.; Zimmermann, R.; Bartsch, R., *Synthesis* **1985**, 662.
10. Iwata, C.; Fujita, M.; Hattori, K.; Uchida, S.; Imanishi, T., *Tetrahedron Lett.* **1985**, *26*, 2221.
11. Arnone, A.; Bravo, P.; Cavicchio, G.; Frigerio, M.; Viani, F., *Tetrahedron* **1992**, *48*, 8523.
12. (a) Posner, G. H.; Tang, P. W., *J. Org. Chem.* **1978**, *43*, 4131. (b) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E., *Synthesis* **1987**, 1088.
13. Hulce, M.; Mallamo, J. P.; Frye, L. L.; Kogan, T. P.; Posner, G. H., *Org. Synth.* **1986**, *64*, 196.
14. Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H., *J. Org. Chem.* **1987**, *52*, 1078.
15. Lee, A. W. M.; Chan, W. H.; Lee, Y. K., *Tetrahedron Lett.* **1991**, *32*, 6861.
16. (a) Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A., *J. Org. Chem.* **1975**, *40*, 1979. (b) Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczyńska, A., *J. Org. Chem.* **1978**, *43*, 473.
17. Moine, G.; Solladié, G., *J. Am. Chem. Soc.* **1984**, *106*, 6097.
18. Mikolajczyk, M.; Perlikowska, W.; Omelańczuk, J.; Cristau, H. J.; Perraud-Darcy, A., *Synlett* **1991**, 913.
19. (a) Carreño, C. M.; García Ruano, J. L.; Urbano, A., *Tetrahedron Lett.* **1989**, *30*, 4003. (b) Carreño, C. M.; García Ruano, J. L.; Mata, J. M.; Urbano, A., *Tetrahedron* **1991**, *47*, 605.
20. Imanishi, T.; Hamano, Y.; Yoshikawa, H.; Iwata, C., *J. Chem. Soc., Chem. Commun.* **1988**, 473.
21. Mioskowski, C.; Solladié, G., *Tetrahedron* **1980**, *36*, 227.
22. (a) Solladié, G.; Matloubi-Moghadam, F.; Luttmann, C.; Mioskowski, C., *Helv. Chim. Acta* **1982**, *65*, 1602. (b) Nokami, J.; Ohtsuki, H.; Sokamoto, Y.; Mitsuoka, M.; Kunieda, N., *Chem. Lett.* **1992**, 1647.
23. Nokami, J.; Mandai, T.; Nishimura, A.; Takeda, T.; Wakabayashi, S.; Kunieda, N., *Tetrahedron Lett.* **1986**, *27*, 5109.
24. Annunziata, R.; Cinquini, M.; Cozzi, F.; Gilardi, A.; Restelli, A., *J. Chem. Soc., Perkin Trans. 1* **1985**, 2289.
25. Cinquini, M.; Manfredi, A.; Molinari, H.; Restelli, A., *Tetrahedron* **1985**, *41*, 4929.
26. Bernardi, A.; Colombo, L.; Gennari, C.; Prati, L., *Tetrahedron* **1984**, *40*, 3769.
27. (a) Carreño, M. C.; García Ruano, J. L.; Rubio, A., *Tetrahedron Lett.* **1987**, *28*, 4861. (b) Carreño, M. C.; García Ruano, J. L.; Pedregal, C.; Rubio, A., *J. Chem. Soc., Perkin Trans. 1* **1989**, 1335. (c) Carreño, M. C.; García Ruano, J. L.; Garrido, M.; Ruiz, M. P.; Solladié, G., *Tetrahedron Lett.* **1990**, *31*, 6653.
28. (a) Schneider, F.; Simon, R., *Synthesis* **1986**, 582. (b) Solladié, G.; Almario, A., *Tetrahedron Lett.* **1992**, *33*, 2477.

29. Solladié, G.; Ghiatou, N., *Tetrahedron: Asymmetry* **1992**, *3*, 33.
30. Carreño, M. C.; García Ruano, J. L.; Dominguez, E.; Pedregal, C.; Rodríguez, J., *Tetrahedron* **1991**, *47*, 10035.
31. (a) Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J., *Synthesis* **1991**, 970. (b) Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A., *J. Org. Chem.* **1991**, *56*, 6998.
32. (a) Kunieda, N.; Nokami, J.; Kinoshita, M., *Bull. Chem. Soc. Jpn.* **1976**, *49*, 256. (b) Solladié, G.; Colobert, F.; Ruiz, P.; Hamdouchi, C.; Carreño, C. M.; García Ruano, J. L., *Tetrahedron Lett.* **1991**, *32*, 3695.
33. López, R.; Carretero, J. C., *Tetrahedron: Asymmetry* **1991**, *2*, 93.
34. Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S., *J. Org. Chem.* **1991**, *56*, 4.

Guy Solladié & Françoise Colobert
University Louis Pasteur, Strasbourg, France

6-Mercapto-4-dibenzofuranol



[101697-54-5] $C_{12}H_8O_2S$ (MW 216.26)
InChI = 1/C12H8O2S/c13-9-5-1-3-7-8-4-2-6-10(15)12(8)14-11(7)9/h1-6,13,15H
InChIKey = KIENRBSPTBMJKU-UHFFFAOYAI

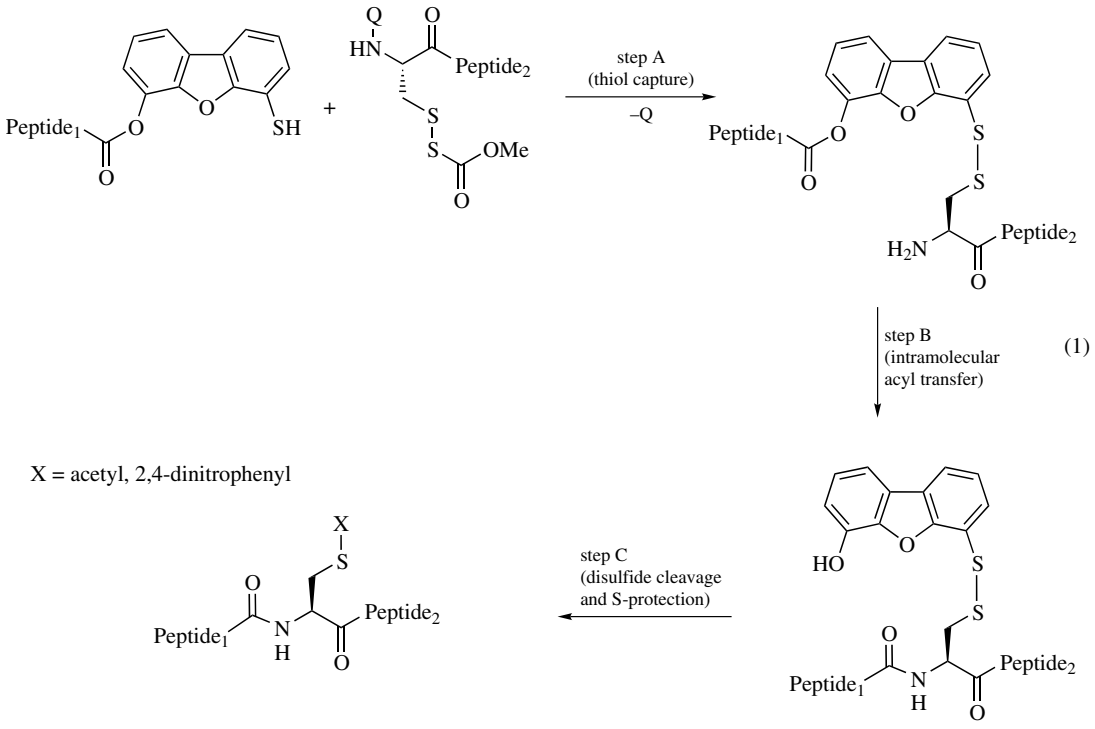
(peptide synthesis by prior thiol capture; solid phase synthesis of polypeptides)

Alternate Name: 4-hydroxy-6-mercaptodibenzofuran.

Introduction. 6-Mercapto-4-dibenzofuranol is a reagent developed specifically[1] as an optimal spacing element to facilitate the intramolecular *O,N* acyl transfer during the second stage of the amide-bond-forming protocol known as the "thiol capture strategy." As a result, it plays a special role in a relatively new solid phase polypeptide synthesis strategy.

Peptide Synthesis by Prior Thiol Capture. A coupling method has been designed to be used at the late stages of fragment condensation syntheses of large peptides that contain cysteine residues spaced 5–20 amino acid residues apart.[1,2] The method takes advantage of an N-terminal cysteine residue. The rationale of the synthesis[3] calls for a template that puts the participating fragments in the right proximity, with the right orientation. The fundamental premise[4] is that a rationally designed system that displays the appropriate distance and orientation of the two reaction centers can induce rapid intramolecular acyl transfer to a weakly basic (p*K*a ca. 7.0) cysteine amino function from a very weakly activated phenyl ester across a span of at least nine atoms. After examination of several templates,[4,5] 6-mercapto-4-dibenzofuranol emerged as the appropriate choice. The thiol capture strategy involves three stages described in eq 1.[1,2]

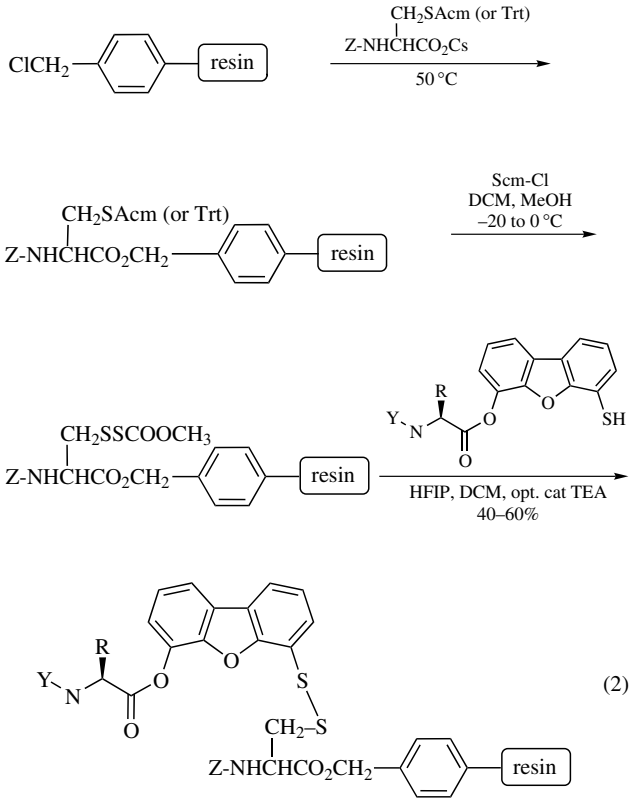
Step A (eq 1)—the disulfide bond formation between a peptide fragment derivatized at the C-terminus as 6-mercaptodibenzofuranyl ester and a peptide fragment bearing an *S*-sulfenylthiocarbonate (Scm) activated cysteine residue at its N-terminus, occurs cleanly and very rapidly at submillimolar concentrations in protic solvents or solvent mixtures. The intramolecular acyl transfer (step B, eq 1) is highly efficient (effective molarity > 1 M),[5,6] to the effect that, for most cases, a very weakly activated phenolic ester can be employed and many quite reactive side-chain functions in R and R′ can be left unprotected.[1] These high reactivity criteria are met best in the protein-solubilizing solvent hexafluoro-2-propanol (HFIP) and its mixtures with water and acetonitrile.[2]



The use of a phenolic ester as anchoring group limits the choice of the protective groups. An appropriate choice is *tert*-butyloxycarbonyl (Boc, trifluoroacetic acid cleavable) for N^{α}-blocking of the amino acid esterified with the phenol and functionalized benzyl groups for side-chain functions.[1] An alternative (preferred in many applications) is *tert*-butyl derived side-chain blocking groups and 2-p-biphenylyl-2-propyloxycarbonyl (Bpoc) for N^{α}-protection.[2]

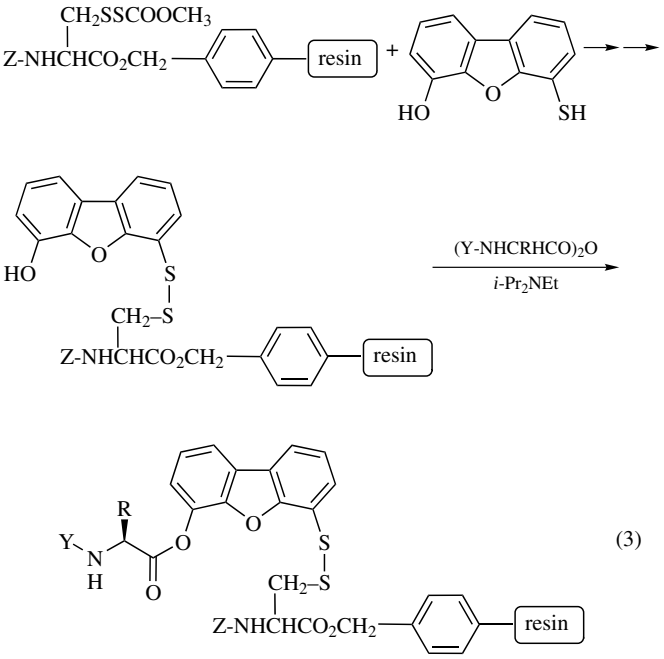
The resin-bound fragment preparation starts with the chlorine displacement from the chloromethylene function on chloromethylated polystyrene by the cesium salt of *Z*-L-Cys(Trt)-OH. The resulting benzyl ester is treated with methoxycarbonyl sulfenyl chloride (Scm-Cl) to form the active intermediate sulfenyl thiocarbonate which is allowed to react with 4-acyloxy-6-mercaptodibenzofuran, preferably in dichloromethane–hexafluoro-2-propanol, with or without catalytic triethylamine to afford the unsymmetrical disulfide (eq 2).[1,7]

An alternative to acetamidomethyl (Acm) and trityl (Trt) for the temporary protection for cysteine is 2,2-dimethylthiazolidine-4-carboxylic acid (H-Dmt-OH, used as the anhydride derived from Boc-Dmt-OH or as Boc-Dmt-OPfp).[8]



(2)

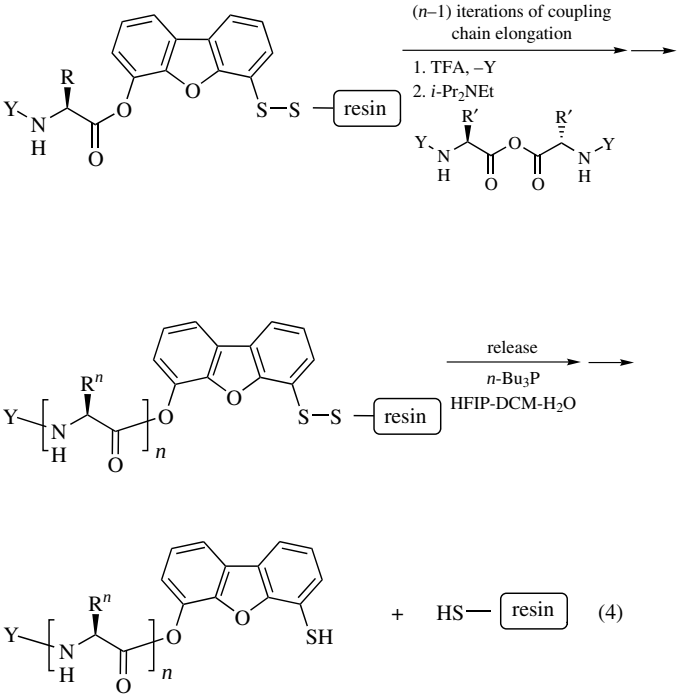
It is often simpler to modify the sequence in eq 2 to the one in which the resin-bound sulfenyl thiocarbonate intermediate is first reacted with 4-hydroxy-6-mercaptodibenzofuran. The free phenol is then acylated by 3–4 equiv of a symmetrical anhydride derived from an N^{α}-carbamate-blocked amino acid in the presence of diisopropylethylamine in dichloromethane (ca. 10–30 min reaction time at 0 °C) (eq 3).[1]



(3)

Y = Boc, Bpoc

A study of the effect of the steric bulk of the side-chain substituent of the acylating agent (R in eq 3) during the second stage of the process (step B, eq 1) revealed that the acyl transfer rates are anomalously low in the case of Pro and especially Val. Also, Asp shows evidence of intramolecular general base catalysis by the neighboring carboxylate group. For Ala, Leu, Lys(Z), Asn, and Arg(9-anthracenesulfonyl) the half-life of the acyl transfer lies between 2 and 4 h when running the reactions in DMSO at room temperature.[9] Racemization during the thiol capture protocol appears to be insignificant.[10]



(4)

The reductive cleavage of the disulfide bond (step C, eq 1) can be performed cleanly and with high reaction rates (almost

instantaneously) by treatment with 1 equiv of tributylphosphine or other trialkylphosphines in dioxane-water at room temperature. An acidic medium (TFA) is required.[1]

Solid Phase Synthesis of Polypeptides. A reaction sequence has been designed for the solid-phase synthesis of a polypeptide esterified at the C-terminus with the phenol functionality in 4-hydroxy-6-mercaptodibenzofuran and resin bound with a disulfide bond (eq 4).[1] There are certain liabilities associated with the method (the lability of the disulfide bond, that of the phenyl ester, cyclization with formation of diketopiperazides after the amine is liberated in the second chain elongation step, etc.). A detailed protocol has been designed to circumvent these issues.[1,11]

Related Reagents. 4-Methoxy-α-[{[(4-methylphenyl)methyl]thio}methyl]benzenemethanamine.

1. Kemp, D. S.; Galakatos, N. G., *J. Org. Chem.* **1986**, *51*, 1821.
2. Fotouhi, N.; Galakatos, N. G.; Kemp, D. S., *J. Org. Chem.* **1989**, *54*, 2803.
3. Kemp, D. S., *Biopolymers* **1981**, *20*, 1793.
4. Kemp, D. S.; Galakatos, N. G.; Bowen, B.; Tan, K., *J. Org. Chem.* **1986**, *51*, 1829.
5. Kemp, D. S.; Carey, R. I.; Dewan, J. C.; Galakatos, N. G.; Kerkman, D.; Leung, S.–L., *J. Org. Chem.* **1989**, *54*, 1589.
6. Kemp, D. S.; Carey, R. I., *J. Org. Chem.* **1993**, *58*, 2216.
7. Brois, S. J.; Pilot, J. F.; Barnum, H. W., *J. Am. Chem. Soc.* **1970**, *92*, 7629.
8. Kemp, D. S.; Carey, R. I., *J. Org. Chem.* **1989**, *54*, 3640.
9. Kemp, D. S.; Galakatos, N. G.; Dranginis, S.; Ashton, C.; Fotouhi, N.; Curran, T. P., *J. Org. Chem.* **1986**, *51*, 3320.
10. McBride, B. J.; Kemp, D. S., *Tetrahedron Lett.* **1987**, *28*, 3435.
11. Fotouhi, N.; Kemp, D. S., *Int. J. Peptide Protein Res.* **1993**, *41*, 153.

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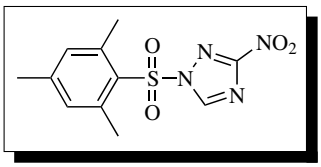
deCode Genetics, Woodridge, IL, USA

1-(Mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT)



[74257-00-4] $C_{11}H_{12}N_4O_4S$ (MW 296.30)
InChI = 1/C11H12N4O4S/c1-7-4-8(2)10(9(3)5-7)20(18,19)14-6-12-11(13-14)15(16)17/h4-6H,1-3H3
InChIKey = SFYDWLYPIXHPML-UHFFFAOYAZ

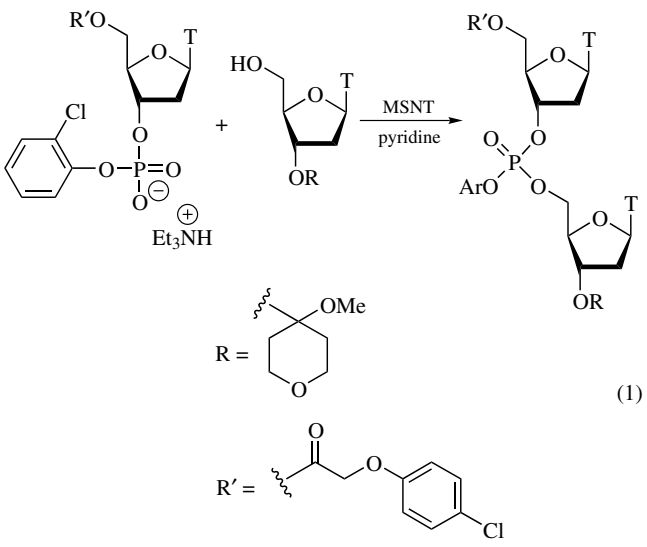
(coupling agent for both solution and solid phase synthesis of oligonucleotides using the phosphotriester method)

Physical Data: mp 132–134 °C.
Solubility: insoluble in H_2O; soluble in CH_2Cl_2, $CHCl_3$, DMF, and pyridine.
Form Supplied in: crystalline solid; commercially available.
Analysis of Reagent Purity: the reagent may be checked by mp or analyzed by ^1H NMR.
Preparative Methods: this reagent can be prepared by the reaction of 3-nitro-1,2,4-triazole (1 equiv) and mesitylsulfonyl chloride (1 equiv) in the presence of triethylamine (1 equiv) in dioxane at 0 °C for 1 h. The product is isolated in 92% yield after crystallization from benzene.[1]
Purity: recrystallization from benzene.
Handling, Storage, and Precautions: this reagent may be an irritant. Avoid contact with the skin. It should be handled under nitrogen and stored below −20 °C.

Synthesis of Oligodeoxyribonucleotides by the Phosphotriester Method. 1-(Mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole-(MSNT) has been widely used as a condensing agent for the synthesis of oligodeoxynucleotides[2,3] by the phosphotriester method.[4]

For example, MSNT readily promotes the coupling of the triethylammonium salt of 5′-*O*-(*p*-chlorophenoxyacetyl)thymidine 3′-(2-chlorophenyl)phosphate and 3′-*O*-methoxytetrahydropyranylthymidine inpyridine (eq 1).[2]

MSNT has been employed as the condensing agent in a continuous-flow, solid-phase synthesis of oligodeoxyribonucleotides using the phosphotriester method (eq 2).[5]

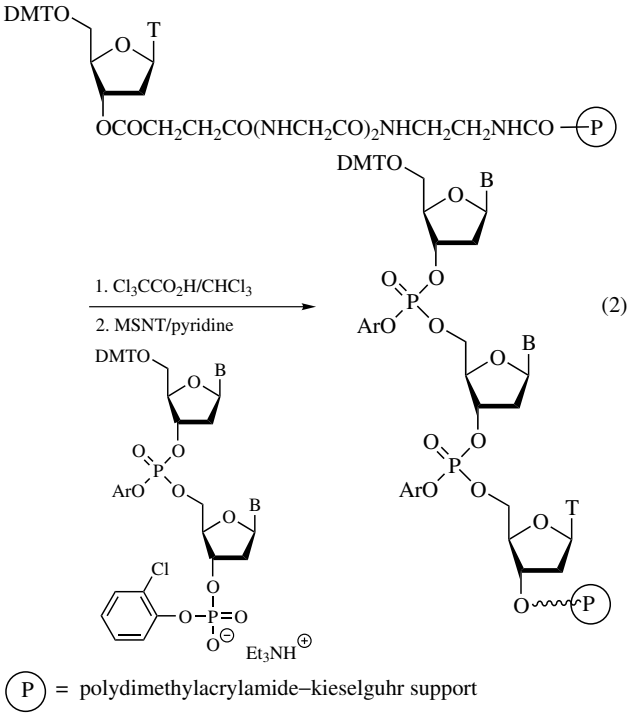


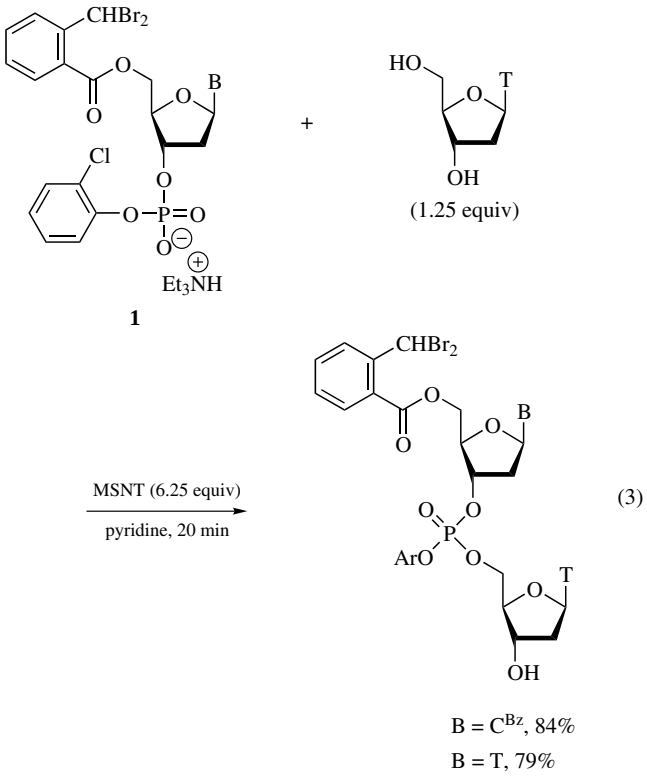
(1)

An additional advantage of using MSNT as the condensing agent is that it is not always necessary to protect the 3′-hydroxy group of the nucleoside. For example, in the presence of MSNT, unprotected thymidine can be coupled to nucleotide **1** regioselectively to give the corresponding 3′-5′ dinucleotide in good yield (eq 3).[3]

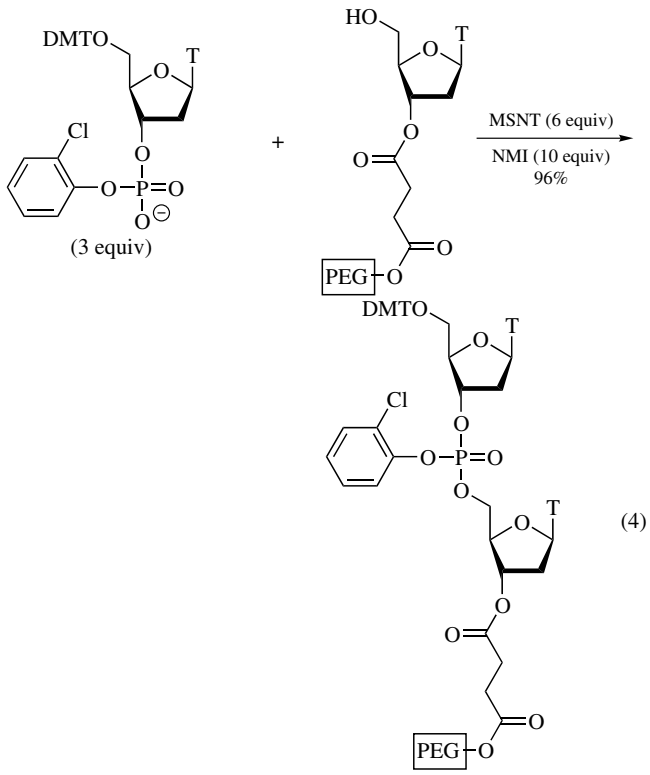
The time required for MSNT-mediated couplings can be considerably shortened by the addition of *N*-methylimidazole (NMI). For example, the time for the monomer (as the triethylammonium salt of the phosphodiester) addition in a solid-phase synthesis of oligodeoxynucleotides performed on controlled pore glass can be reduced to less than 10 min when MSNT is used in combination with NMI.[6] A large-scale soluble polymer

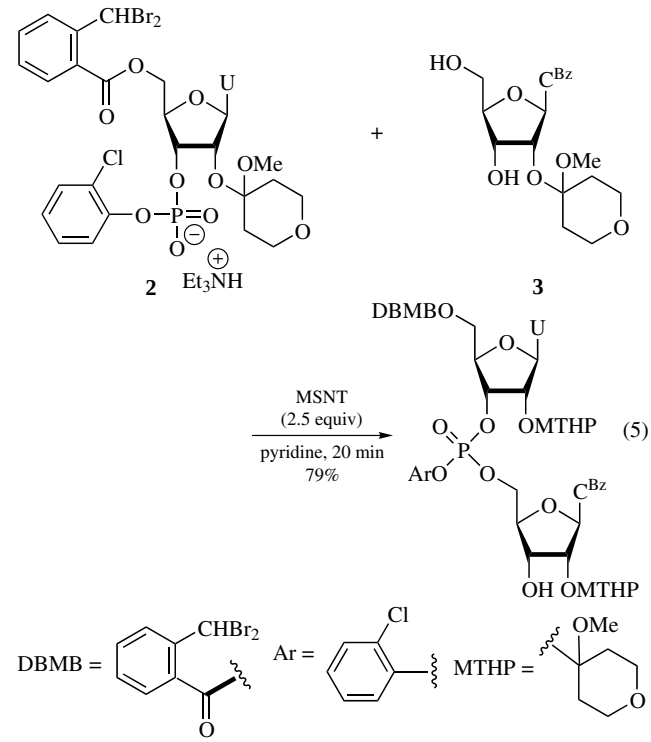
PEG-supported oligodeoxynucleotide synthesis has been developed using MSNT/NMI as the coupling agent as shown in eq 4 for the synthesis of d(TpT).[7] This synthesis can be extended to higher oligomers such as d(TAGCGCTA).



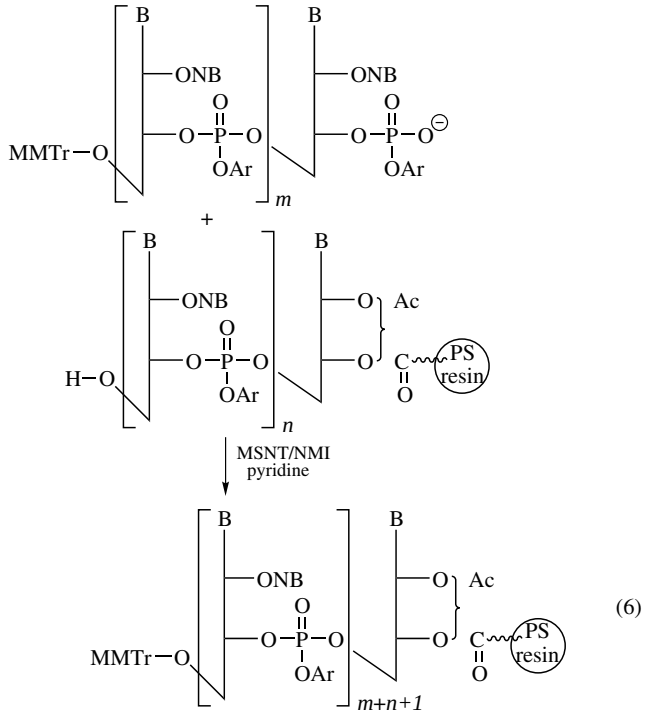


Synthesis of Oligoribonucleotides by the Phosphotriester Method. The use of MSNT as the condensing agent has also been extended to both the solution and the solid-phase synthesis of oligoribonucleotides. For example, the uridine-derived mononucleotide **2** couples to 2′-*O*-methoxytetrahydropyranyl-4-*N*-benzoylcytidine (**3**) in the presence of MSNT in pyridine in just 20 min to give the partially protected dinucleotide phosphate in 79% yield (eq 5).[1] Cyclic oligoribonucleotides can also be synthesized by the phosphotriester method using MSNT as the condensing agent.[8]





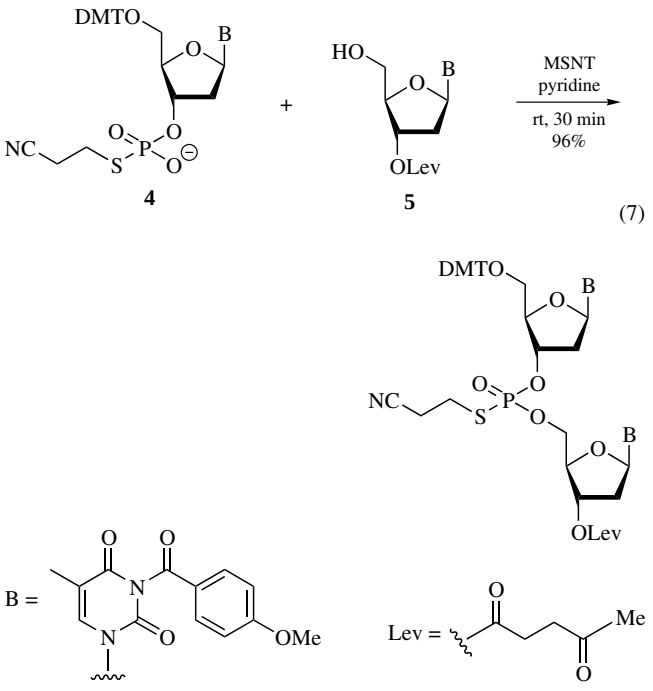
MSNT has been used for the solid-phase synthesis of oligonucleotides on cross-linked polystyrene (eq 6).[9] Best coupling result can be obtained by adding NMI as a catalyst, which not only increases the average condensation yield but also allows the dinucleotide phosphate to be coupled to the 5′-OH group of the growing oligonucleotide chain on the solid support.



(6)

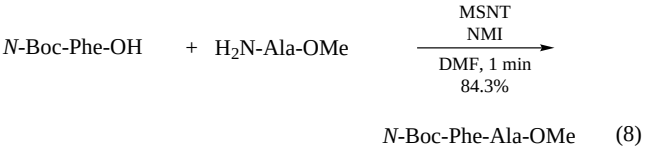
NB = *o*-nitrobenzyl
Ar = *o*-chlorophenyl; *m* = 0, 1

Formation of Nucleoside Phosphorothiolates. MSNT also promotes the formation of nucleoside phosphorothiolate triesters.[10,11] As shown in eq 7, the coupling of nucleoside phosphorothiolate **4** and nucleoside **5** is rapid in the presence of MSNT, giving the dinucleoside phosphorothiolate in excellent yield.[10]



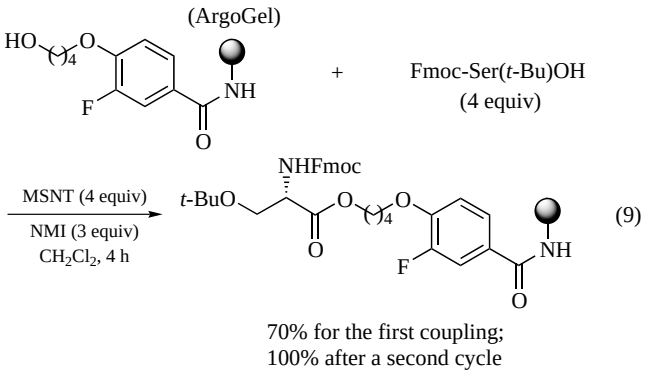
(7)

Esterification, Amide Bond Formation, and Peptide Synthesis. In the presence of NMI, MSNT can be used as a coupling agent for amide bond formation[12] both in solution and in solid-phase peptide synthesis. The dipeptide Phe-Ala is formed very rapidly in 84.3% yield with virtually no racemization using MSNT as the coupling agent in the presence of NMI (eq 8).[12] The combination of MSNT and NMI can also be used for peptide formation on solid supports.[13]



(8)

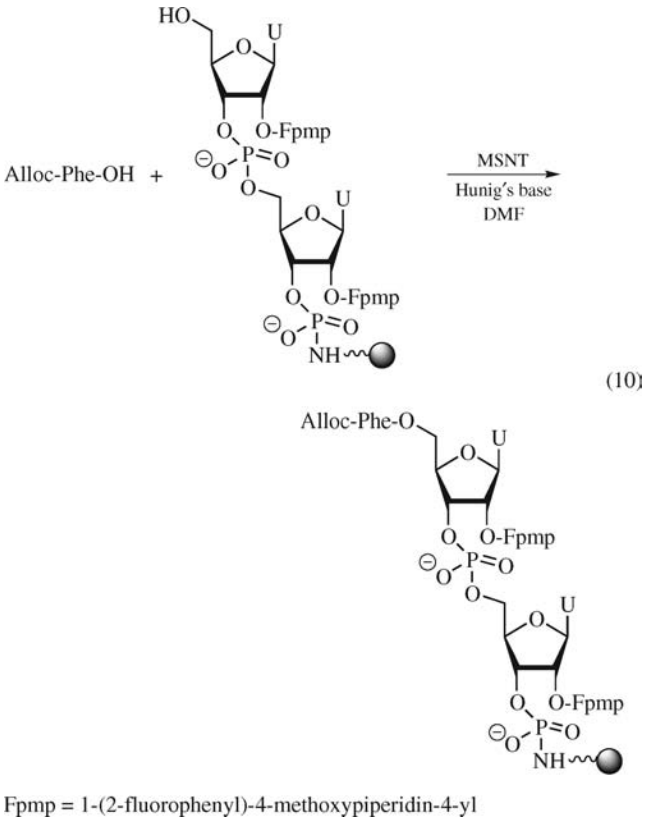
In the presence of NMI, MSNT can be used as an efficient coupling agent for ester bond formation. For example, Fmoc-amino acids (Fmoc-AA) can be anchored to hydroxyl-functionalised solid supports using MSNT as the coupling agent in the presence of NMI.[14] Best results are obtained with the ratio Fmoc-AA:MSNT:NMI = 1:1:0.75. The MSNT:NMI method proved to be of general utility and gives better results than the conventional symmetrical anhydride/DMAP method. This protocol has been applied to the anchoring of Fmoc-Ser(*t*-Bu)OH onto ArgoGel resin modified with a fluorine-labeled alcohol linker (eq 9).[15]



(9)

70% for the first coupling;
100% after a second cycle

Aminoacylation of the 5′-hydroxyl group of partially protected oligouridylic acids on controlled pore glass support is achieved with high yield by using MSNT as the condensing agent in the presence of Hunig's base (eq 10).[16] The same reactions using other coupling methods, including DCC/HOBT, DCC/DMAP, or PPh_3/DIAD, either failed or gave much lower conversion.



1. Jones, S. S.; Rayner, B.; Reese, C. B.; Ubasawa, A.; Ubasawa, M., *Tetrahedron* **1980**, *36*, 3075.
2. Reese, C. B.; Titmas, R. C.; Yau, L., *Tetrahedron Lett.* **1978**, *19*, 2727.
3. Chattopadhyaya, J. B.; Reese, C. B., *Tetrahedron Lett.* **1979**, *20*, 5059.
4. Reese, C. B., *Tetrahedron* **1978**, *34*, 3143.
5. Gait, M. J.; Matthes, H. W. D.; Singh, M.; Titmas, R. C., *J. Chem. Soc., Chem. Commun.* **1982**, 37.
6. Sproat, B. S.; Bannwarth, W., *Tetrahedron Lett.* **1983**, *24*, 5771.
7. Bonora, G. M.; Scremin, C. L.; Colonna, F. P.; Garbesi, A., *Nucleosides Nucleotides* **1991**, *10*, 269.
8. De Napoli, L.; Galeone, A.; Mayol, L.; Messere, A.; Piccialli, G.; Santacroce, C., *J. Chem. Soc., Perkin Trans. 1* **1993**, 747.
9. Tanaka, T.; Orita, M.; Uesugi, S.; Ikehara, M., *Tetrahedron* **1988**, *44*, 4331.
10. Reese, C. B.; Song, Q.; Rao, M. V.; Beckett, I., *Nucleosides Nucleotides* **1998**, *17*, 451.
11. Reese, C. B.; Song, Q., *Nucleic Acids Res.* **1999**, *27*, 2672.
12. Bannwarth, W., *Chimia* **1987**, *41*, 302.
13. Jorba, X.; Albericio, F.; Grandas, A.; Bannwarth, W.; Giralt, E., *Tetrahedron Lett.* **1990**, *31*, 1915.
14. Blankemeyer-Menge, B.; Nimtz, M.; Frank, R., *Tetrahedron Lett.* **1990**, *31*, 1701.
15. Mogemark, M.; Elofsson, M.; Kihlberg, J., *Org. Lett.* **2001**, *3*, 1463.
16. Tetzlaff, C. N.; Richert, C., *Tetrahedron Lett.* **2001**, *42*, 5681.

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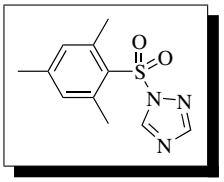
Mesitylsulfonyl-1*H*-1,2,4-triazole



[54230-59-0] $C_{11}H_{13}N_3O_2S$ (MW 251.34)

InChI = 1/C11H13N3O2S/c1-8-4-9(2)11(10(3)5-8)17(15,16)14-7-12-6-13-14/h4-7H,1-3H3

InChIKey = XNKYPZJMRHXJJQ-UHFFFAOYAL

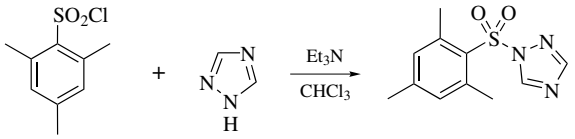
(reagent for phosphate activation[1] and nucleotide condensation[2])

Alternate Name: MST.

Physical Data: mp 135 °C.

Form Supplied in: solid; widely available from commercial sources.

Preparative Method: readily prepared by the reaction of equimolar ratios of mesitylenesulfonyl chloride, 1,2,4-triazole, and triethylamine in a chloroform solution (eq 1).[3]



(1)

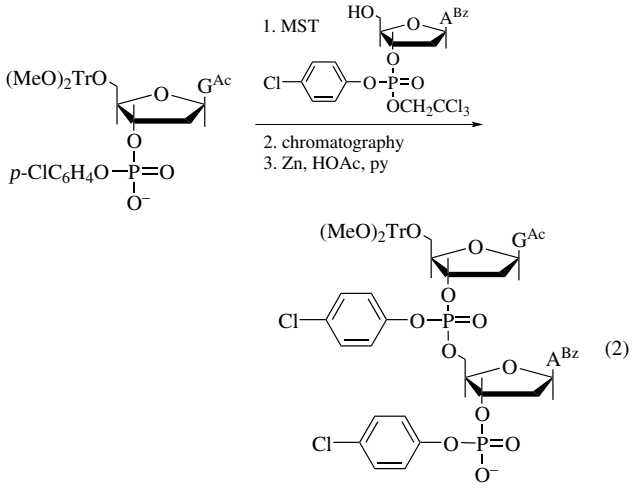
Purification: recrystallization from benzene.

Phosphate Activator. MST was shown to be an effective catalyst for the phosphorylation of a 5′-protected mononucleoside.[1] MST was stirred with *p*-chlorophenyl phosphorodichloridate and triethylamine and the resulting agent was used directly for the phosphorylation of 5′-protected nucleosides in 70–85% yields.

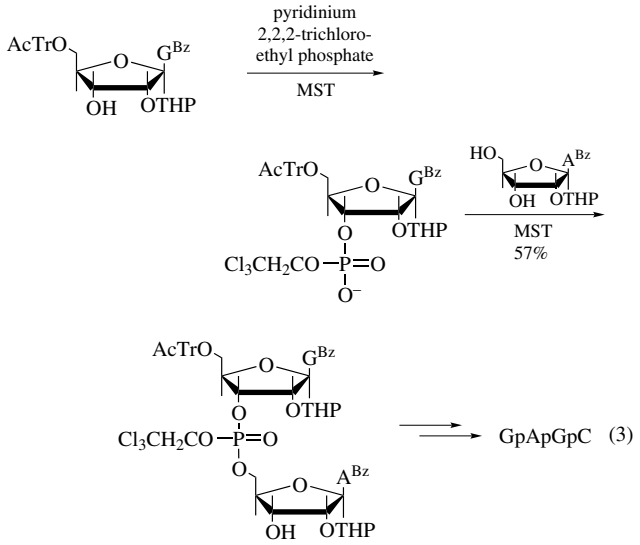
Oligonucleotide Synthesis. As originally reported, the triester approach to the formation of oligonucleotides involved using triisopropylbenzenesulfonyl chloride (TPS) as a condensing agent for a 5′–3′ internucleotide condensation. Since that time, many modifications of this procedure have been reported, including (i) using a stepwise phosphorylation then condensation procedure,[2] (ii) synthesizing the oligonucleotide in the 3′–5′ rather than the 5′–3′ direction,[2] (iii) varying the protecting groups used in these transformations, and (iv) changing the condensing agent. MST is one of the more recently reported condensing agents for the synthesis of oligonucleotides through the formation of 3′,5′-internucleotide bonds via the triester approach. The initial report of the use of MST was in the synthesis of a fully protected dinucleotide (eq 2).[3]

A follow-up full paper by the same authors extended this methodology to the synthesis of hexanucleotides by an iterative phosphorylation and condensation sequence.[1] This paper also kinetically compared this reagent to some of the previously used condensing agents. It was reported that although the reaction using MST was significantly slower than that using TPS, the reaction mixture was much cleaner and the yields were much higher. This was especially true for synthesis of nucleotides that

contained purine units, which were formed only in low yields when TPS was employed as the condensing agent, perhaps due to the liberation of HCl from the reagent. MST was also employed as the condensing reagent in the synthesis of 3′,5′-bisphosphorylated oligonucleotides.[4]



Oligoribonucleotide Synthesis. Subsequent work showed that this reagent was useful in the synthesis of the less stable oligoribonucleotides as well as deoxyribonucleotides.[5] In the same iterative manner as described above for deoxyribonucleotide synthesis, the tetrameric ribonucleotide GpApGpC was formed (eq 3).



Yields were reported to be significantly improved over previously described methods that employed TPS as the condensing agent, especially in the coupling of purine residues. Note again that MST can also be used in the phosphorylation step of the condensation sequence. MST was also used as a condensing agent for the synthesis of 2′(3′)-*O*-aminoacyl triribonucleoside diphosphates.[6]

1. Katagiri, N.; Itakura, K.; Narang, S. A., *J. Am. Chem. Soc.* **1975**, *97*, 7332.
2. Itakura, K.; Katagiri, N.; Bahl, C. P.; Wightman, R. H.; Narang, S. A., *J. Am. Chem. Soc.* **1975**, *97*, 7327.
3. Katagiri, N.; Itakura, K.; Narang, S. A., *J. Chem. Soc. (C)* **1974**, 325.
4. Ikehara, N.; Oshie, K.; Hasegawa, A.; Ohtsuka, E., *Nucleic Acids Res.* **1981**, *9*, 2003.
5. England, T. E.; Nielson, T., *Can. J. Chem.* **1976**, *54*, 1714.
6. Kumar, G.; Chladek, S., *Tetrahedron Lett.* **1981**, *22*, 827.

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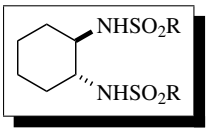
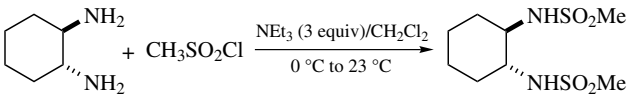
(*R*,*R*)-1,2-(Methanesulfonamido)-cyclohexane



1a R = Me
[122833-60-7]
InChI = 1/C8H12F6N2O4S2/c9-7(10,11)21(17,18)15-5-3-1-2-4-6(5)16-22(19,20)8(12,13)14/h5-6,15-16H,1-4H2/t5-,6-/m1/s1
InChIKey = GKSGSDYYIYURPD-PHDIDXHHBV
1b R = CF_3
[290833-56-6]
InChI = 1/C14H30N2O4S2/c1-3-5-11-21(17,18)15-13-9-7-8-10-14(13)16-22(19,20)12-6-4-2/h13-16H,3-12H2,1-2H3/t13-,14-/m1/s1
InChIKey = JUGCCRUREILMAM-ZIAGYGMSBX
1c R = *n*-Bu
[155237-72-2]
InChI = 1/C18H20N4O8S2/c23-21(24)13-5-9-15(10-6-13)31(27,28)19-17-3-1-2-4-18(17)20-32(29,30)16-11-7-14(8-12-16)22(25)26/h5-12,17-20H,1-4H2/t17-,18-/m1/s1
InChIKey = AHFPEDLBFJTANO-QZTJIDSGBM
1d R = 4-NO_2Ph
[166109-85-9]
InChI = 1/C12H26N2O4S2/c1-9(2)19(15,16)13-11-7-5-6-8-12(11)14-20(17,18)10(3)4/h9-14H,5-8H2,1-4H3/t11-,12-/m1/s1
InChIKey = WBVDMPSXIZEBDT-VXGBXAGGBF
1e R = *i*-Pr
[263019-97-2]
InChI = 1/C24H34N2O4S2/c1-15-11-17(3)23(18(4)12-15)31(27,28)25-21-9-7-8-10-22(21)26-32(29,30)24-19(5)13-16(2)14-20(24)6/h11-14,21-22,25-26H,7-10H2,1-6H3/t21-,22-/m1/s1
InChIKey = IQJCBLZVBZRSFZ-FGZHOGPDBX
1f R = mesityl
[122833-58-3] $C_8H_{18}N_2O_4S_2$ (MW 270.36)
InChI = 1/C8H18N2O4S2/c1-15(11,12)9-7-5-3-4-6-8(7)10-16(2,13)14/h7-10H,3-6H2,1-2H3/t7-,8-/m1/s1
InChIKey = JUWLQVLCYRNWSV-HTQZYQBOBH

(catalyst for organozinc-mediated additions to aldehydes,[1] catalyst for Simmons–Smith type cyclopropanation of allylic alcohols[2])

Physical Data: mp 157 °C; $[\alpha]_D^{20}$ −20.1 (*c* 3.07, pyridine).
Solubility: soluble in most organic solvents except hydrocarbons.
Form Supplied in: white solid.
Preparative Methods: The enantiopure sulfonamide **1a** is prepared via sulfonylation of (*R*,*R*)-1,2-diaminocyclohexane **2** in the presence of an excess of triethylamine (eq 1).[3] Use of excess amine base is essential for obtaining a high yield of the bis-sulfonamide. Synthesis of related bis-sulfonamides is easily accomplished by substituting the desired sulfonyl chloride in the former procedure. Recrystallization of the bis-sulfonamide **1a** from hexane/ethyl acetate and drying over P_2O_5 allows for isolation of the analytically pure reagent. Methanesulfonyl chloride and (*R*,*R*)-1,2-diaminocyclohexane **2** are commercially available from a number of sources. However it should be noted that racemic 1,2-diaminocyclohexane **2** can be resolved via formation of the tartrate salt.[4] Typically, the diamine can be obtained in >99:1 enantiomeric ratio (er) after two crystallizations from water. Determination of the enantiopurity of the diamine is accomplished via formation of the bis-3-toluyl amide and analysis via chiral stationary phase HPLC (Chiralcel AD; hexane/*i*-PrOH; 95:5, 1.0 mL min^{-1}).

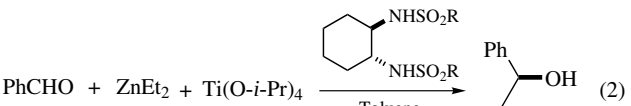


2 1 equiv — 2.6 equiv — **1a** 96% yield (1)

Handling, Storage, and Precaution: The sulfonamide is a shelf-stable, non-hygroscopic compound which does not require special precautions for storage or handling.

Introduction. The 1,2-bis-(methanesulfonamido)-cyclohexane **1a** is an important member of a larger class of C_2-symmetric bis-sulfonamide ligands which have had a powerful impact on the field of organozinc chemistry.[1,2] The success of these ligands is, in part, due to the straightforward installation of a variety of sulfonamide groups, providing access to a wide array of sterically and electronically diverse ligands.

Additions to Aldehydes. Alkylation of aromatic and aliphatic aldehydes with a combination of titanium tetraisopropoxide, Ti(O-*i*-Pr)$_4$, and diethylzinc, $ZnEt_2$, in the presence of a catalytic amount of the bis-sulfonamide **1a** leads to formation of (*S*)-1-phenyl-1-propanol **4** with high enantioselectivity (eq 2, Table 1).[5] Use of the (*R*,*R*)-1,2-(trifluoromethanesulfonamido)-cyclohexane **1b** [CAS 122833-60-7] allows for an equally selective reaction, but at exceptionally low catalyst loadings. In the case of aromatic aldehydes, these reactions are fairly rapid, requiring at most 2 hours to reach full conversion.



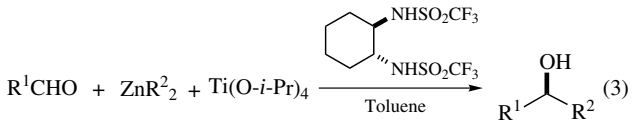
3 1 equiv — 1.2 equiv — 1.2 equiv — **4** (2)

Through the use of the bis-sulfonamide **1b**, the scope of the reaction has been expanded to include a larger number of aldehydes and organozinc reagents (Table 2). High yields and selectivities are obtained in the alkylations of conjugated aldehydes (**5**) as well as simple aliphatic aldehydes (**7**,**9**). The broad scope of this reaction with respect to the electrophile contrasts the slightly limited scope of the reaction when considering the structure of the nucleophile. The use of small alkylzinc reagents, such as dimethylzinc, leads to a depressed selectivity (entry 4). However, the use of larger alkylzinc reagents still provides the exceptional selectivity observed in the case of diethylzinc (entries 5 and 6) .

Table 1 Alkylation of benzaldehyde in the presence of sulfonamide catalysts **1a–b**

R	Cat. loading (%)	Temp. (°C)	Yield (%)	**4** (er)
Me (**1a**)	4	23	90	95:5
Me (**1a**)	4	0	97	83:17
CF_3 (**1b**)	4	0	99	99:1
CF_3 (**1b**)	0.05	−20	97	99:1

er, enantiomeric ratio.



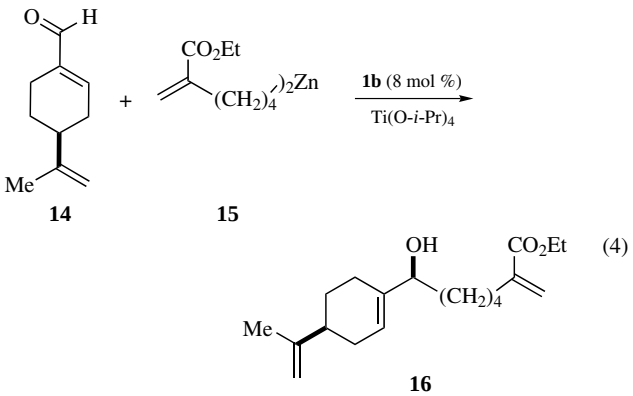
(3)

Table 2 Substrate scope in the alkylation of aldehydes with sulfonamide **1b**

Entry	R^1	R^2	Loading (%)	Temp. (°C)	Yield (%)	Product	er Product	er
1	PhCH=CH (**5**)	CH_3CH_2	2	−50	85	**6**	>99:1	
2	$PhCH_2CH_2$ (**7**)	CH_3CH_2	1	0	95	**8**	96:4	
3	*n*-C_5H_{11} (**9**)	CH_3CH_2	4	−20	87	**10**	>99:1	
4	Ph (**3**)	CH_3	4	0	99	**11**	86:14	
5	Ph (**3**)	*n*-C_4H_9	2	−20	98	**12**	99:1	
6	Ph (**3**)	*n*-C_5H_{11}	2	−50	99	**13**	>99:1	

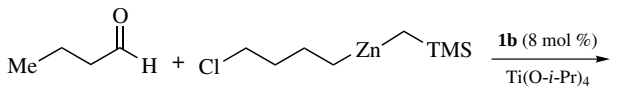
er, enantiomeric ratio.

The scope of the reactive partners has been fully explored and expanded to include a diversity of functionalized organozinc reagents. Preparation of the functionalized organozinc reagent proceeds via hydroboration and boron-zinc exchange of a simple terminal alkene. The resulting organozinc reagent can then be used in an identical manner to that shown above. In the presence of <10 mol % of catalyst **1b**, high yields and selectivities can be obtained (eq 4).[6] One drawback of this method is that 50% of the

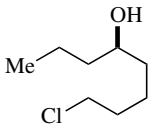


14 **15** **16** 71% yield (93:7 er) (4)

starting alkene must be sacrificed. However, recent reports have revealed that use of a mixed organozinc species, which is accessible by disproportionation of two symmetric organozinc reagents, obviates this wasteful complication (eq 5).[7]



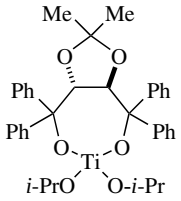
17 **18**



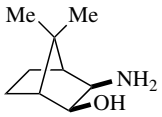
(5)

19
86% yield (97:3 er)

Comparable selectivity can be obtained in the alkylation of benzaldehyde **3** with diethylzinc using the titanium TADDOL complex **20** (>99:1 er) or 3-*exo*-(dimethylamino)isoborneol, **21** (>99:1 er), although both methods employ higher catalyst loadings.[8,9] While benzaldehyde is illustrative, the substrate scope is equally broad in the case of these two catalysts.

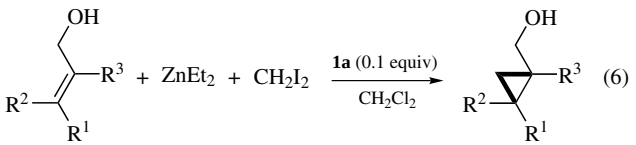


20 (95:5 er)



21 (>99:1 er)

Cyclopropanation of Allylic Alcohols. Simmons–Smith type cyclopropanation of the allylic alcohol **22** in the presence of a catalytic amount of the bis-sulfonamide **1a** leads to formation of the corresponding cyclopropane **23** in high yield and selectivity (eq 6, Table 3).[10] The reaction is rapid (<1 h) and can be performed at low temperature (either 0 °C or −20 °C). Substrate scope encompasses both di- and tri-substituted allylic alcohols (**24** and **26**). However, substitution at the 2 position, as in **28**, leads to a drastic decrease in selectivity. The presence of additional oxygenated functionality (**30**) in the proximity of the alkene also lessens selectivity.[11] The method is limited to the cyclopropanation of allylic alcohols. Other alkene-containing substrates, such as allylic ethers, homo-allylic alcohols and allylic carbamates, do not react with high selectivity.



(6)

1 equiv 3.1 equiv 2 equiv

The optimal procedure calls for a three-flask protocol which segregates the individual reactive components. Pre-formation of the zinc alkoxide, zinc sulfonamide complex and the cyclopropanation reagent, $Zn(CH_2I)_2$, by combination of diethylzinc with the allylic alcohol, bis-sulfonamide and diiodomethane, respectively, is essential for high selectivity and reproducibility. While the individual reaction components are soluble in halogenated solvents such as dichloromethane, the zinc sulfonamide complex is a highly insoluble species which is prone to aggregation. Because of the nature of the zinc carbenoid, a heterogenous reaction is always observed. None of the related bis-sulfonamide catalysts shown in Table 4 are able to dissolve the precipitate. Still, a survey of catalyst structure reveals that large variations in sulfonamide structure can be tolerated without compromising selectivity (entries 1 and 2).[10,12] Bulky sulfonamide groups, however, clearly interfere with the selective cyclopropanation process (entries 3 and 4).

Table 3 Substrate generality in the cyclopropanation using sulfonamide **1a**

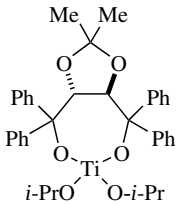
Entry	Substrate	R^1	R^2	R^3	Yield (%)	Product	er
1	**22**	Ph	H	H	92	**23**	95:5
2	**24**	$PhCH_2CH_2$	H	H	88	**25**	95:5
3	**26**	Ph	Me	H	92	**27**	95:5
4	**28**	Ph	H	Me	91	**29**	51:49
5	**30**	$BnOCH_2$	H	H	70	**31**	68:32

er, enatiomeric ratio.

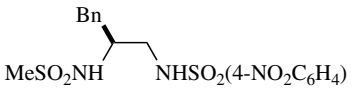
Table 4 Selectivity of various sulfonamides in the cyclopropanation of **22**

Entry	R	Compound	**23** (er)
1	*n*-Bu	**1c**	92:8
2	$4\text{-}NO_2C_6H_4$	**1d**	89:11
3	*i*-Pr	**1e**	86:14
4	$2,4,6\text{-}MeC_6H_2$	**1f**	62:38

This method is comparable to similar catalytic Simmons–Smith-type methods employing the titanium TADDOL catalyst **20** (95:5 er) or the C_1-symmetric bis-sulfonamide catalyst **32** (93:7 er) for the cyclopropanation of the allylic alcohol **22** (eq 6).[13,14] However, due to the preliminary nature of these earlier investigations, substrate scope and generality have not been extensively documented. All of the aforementioned methods are limited by their dependence on the allylic alcohol functionality. Only one method for Simmons–Smith-type cyclopropanation of other substrate classes has been developed. Use of a stoichiometric, chiral dioxaborolane [CAS 161344-85-0] additive allows for selective cyclopropanation of allylic ethers, homo-allylic alcohols and allylic carbamates.[15]



20 (95:5 er)



32 (93:7 er)

1. (a) Pu, L.; Yu, H. B., *Chem. Rev.* **2001**, *101*, 757. (b) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Heidelberg, 1999, Ch. 26.1, p 911.
2. (a) Charette, A. B.; Beauchemin, A., *Org. React.* **2001**, *58*, 1. (b) Charette, A. B.; Lebel, H. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E.

N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Heidelberg, 1999, Ch. 16.3, p 581.
3. Denmark, S. E.; Christenson, B. L.; O'Connor, S. P., *Tetrahedron Lett.* **1995**, *36*, 2219.
4. (a) Glasbøl, F.; Steenbøl, P.; Søndergaard-Sørenson, B., *Acta Chem. Scand.* **1972**, *26*, 3605. (b) Whitney, T. A., *J. Org. Chem.* **1980**, *45*, 4214.
5. (a) Yoshioka, M.; Kawakita, T.; Ohno, M., *Tetrahedron Lett.* **1989**, *30*, 1657. (b) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691.
6. Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P-Y.; Knochel, P., *J. Org. Chem.* **1996**, *61*, 8229.
7. (a) Lutz, C.; Knochel, P., *J. Org. Chem.* **1997**, *62*, 7895. (b) Lutz, C.; Jones, P.; Knochel, P., *Synthesis* **1999**, 312.
8. (a) Schmidt, B.; Seebach, D., *Angew. Chem., Int. Ed. Eng.* **1991**, *30*, 99. (b) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M., *Tetrahedron* **1994**, *50*, 4363.
9. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R., *J. Am. Chem. Soc.* **1986**, *108*, 6071.
10. (a) Denmark, S. E.; O'Connor, S. P., *J. Org. Chem.* **1997**, *62*, 3390. (b) Denmark, S. E.; O'Connor, S. P., *J. Org. Chem.* **1997**, *62*, 584.
11. Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayahsi, S., *Tetrahedron* **1995**, *51*, 12013.
12. Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S., *Tetrahedron Lett.* **1992**, *33*, 2575.
13. Charette, A. B.; Brochu, C., *J. Am. Chem. Soc.* **1995**, *117*, 11367.
14. Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett.* **1997**, *38*, 1423.
15. (a) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C., *J. Am. Chem. Soc.* **1998**, *120*, 11943. (b) Charette, A. B.; Lebel, H.; Gagnon, A., *Tetrahedron* **1999**, *55*, 8845.

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Methanesulfonic Anhydride

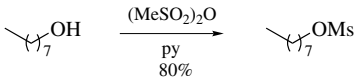
$(MeSO_2)_2O$

[7143-01-3] $C_2H_6O_5S_2$ (MW 174.22)
InChI = 1/C2H6O5S2/c1-8(3,4)7-9(2,5)6/h1-2H3
InChIKey = IZDROVVXIHRYMH-UHFFFAOYAS

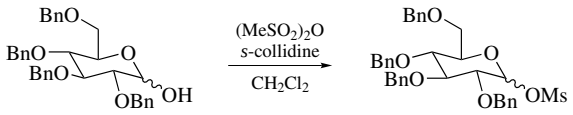
(preparation of sulfonates[1–3])

Physical Data: mp 69–70 °C; bp 125 °C/4 mmHg.
Solubility: sol organic solvents.
Form Supplied in: off-white powder; widely available.
Purification: can be recrystallized from diethyl ether.
Handling, Storage, and Precautions: corrosive; moisture sensitive. Store in a cool, dry place.

Sulfonate Formation. The preparation of an alkyl methanesulfonate from an alcohol can be achieved by treatment of an alcohol with methanesulfonic anhydride in the presence of pyridine or 2,4,6-collidine (eq 1).[1] The use of methanesulfonic anhydride rather than methanesulfonyl chloride eliminates the formation of small amounts of alkyl chlorides which occurs when methanesulfonyl chloride is used. Methanesulfonic anhydride, however, does not work very well for the formation of mesylates of unsaturated alcohols. Glycosyl mesylates (eq 2)[2,3] and 11-*O*-methylsulfonylerythromycins[4] have been synthesized using methanesulfonic anhydride.

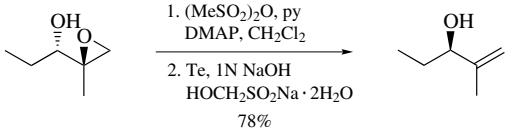


(1)



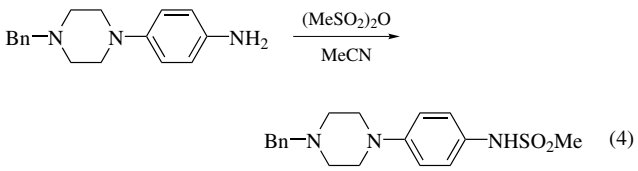
(2)

Glycosyl mesylates can be converted to glycosides by treatment with alcohols, and have also been used as intermediates in the synthesis of oxyglycals. Preparation of methyl ethers by solvolysis of mesylates in methanol has been reported.[5] Treatment of glycidols with methanesulfonic anhydride yields the epoxy mesylate which can then be treated with tellurium to produce the allyl alcohol (eq 3).[6]



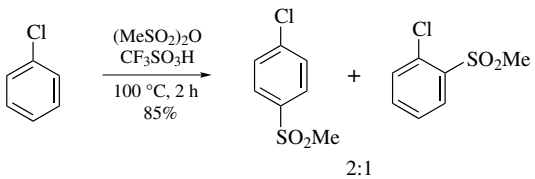
(3)

Sulfonamide Formation. Treatment of amines with methanesulfonic anhydride in acetonitrile yields the methanesulfonamide (eq 4).[7] Sulfonamides are versatile protecting groups for the amino group, displaying good stability to both acidic and basic conditions. The sulfonamide group can be cleaved by lithium aluminum hydride or dissolving metal reductions. Methanesulfonamides are also present in some biologically active molecules.

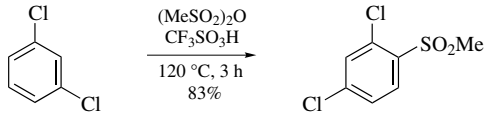


(4)

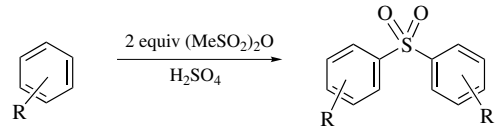
Sulfone Formation. Friedel–Crafts methylsulfonation of benzene or substituted benzenes can be achieved via treatment with methanesulfonic anhydride in the presence of a Lewis acid catalyst (eqs 5 and 6).[8,9] Unlike methanesulfonyl chloride, which sulfonates only activated benzenes, treatment of deactivated benzenes with methanesulfonic anhydride produces the desired sulfones in good yields.[8,10] Diaryl sulfones can be formed using methanesulfonic anhydride and sulfuric acid (eq 7).[11]



(5)



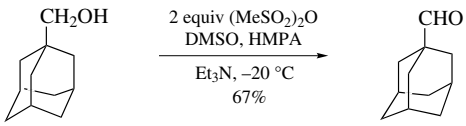
(6)



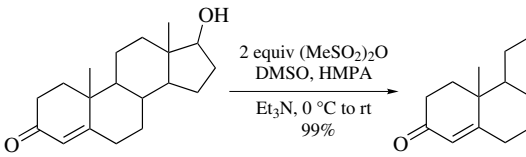
(7)

R = H, Et, Me, OEt, OMe

Oxidation of Alcohols. Primary and secondary alcohols can be oxidized to aldehydes and ketones in good yields via treatment with methanesulfonic anhydride and dimethyl sulfoxide in HMPA (eqs 8 and 9). Dichloromethane can be substituted as the solvent, but the use of HMPA leads to cleaner products. Methanesulfonic anhydride works especially well for the conversion of primary alcohols to aldehydes.[12] Benzylic aldehydes can also be formed using this method.



(8)



(9)

Related Reagents. Acetic Anhydride; Benzoyl Chloride; Dimethyl Sulfoxide–Methanesulfonic Anhydride; Methanesulfonyl Chloride; *p*-Toluenesulfonyl Chloride; Trifluoroacetic Anhydride.

1. Mangold, H. K., *Chem. Phys. Lipids* **1973**, *10*, 354.
2. Leroux, J.; Perlin, A. S., *Carbohydr. Res.* **1978**, *67*, 163.
3. Jones, G. S.; Scott, W. J., *J. Am. Chem. Soc.* **1992**, *114*, 1491.
4. Tadanier, J.; Martin, J. R.; Egan, R. S.; Goldstein, A. W.; Stanaszek, R. S.; Hirner, E.; Fischer, F., *J. Org. Chem.* **1974**, *39*, 2495.
5. Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R., *J. Am. Chem. Soc.* **1980**, *102*, 2838.
6. Discordia, R. P.; Dittmer, D. C., *J. Org. Chem.* **1990**, *55*, 1414.
7. Lis, R.; Morgan, T. K., Jr.; Marisca, A. J.; Gomez, R. P.; Lind, J. M.; Davey, D. D.; Phillips, G. B.; Sullivan, M. E., *J. Med. Chem.* **1990**, *33*, 2883.
8. (a) Fieser, L. F.; Fieser, M., *Fieser & Fieser* **1967**, *1*, 667. (b) Fieser, M., *Fieser & Fieser* **1990**, *15*, 201.
9. Olah, G. A.; Kobayashi, S.; Nishimura, J., *J. Am. Chem. Soc.* **1973**, *95*, 564.
10. Ono, M.; Nakamura, Y.; Sato, S.; Itoh, I., *Chem. Lett.* **1988**, 395.
11. (a) Tyobeka, T. E.; Weigel, H., *S. Afr. J. Chem.* **1990**, *43*, 71. (b) Tyobeka, T. E.; Hancock, R. A.; Weigel, H., *J. Chem. Soc., Chem. Commun.* **1980**, 114.
12. Albright, J. D., *J. Org. Chem.* **1974**, *39*, 1977.

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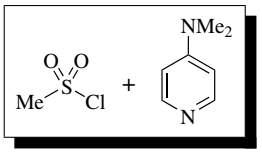
Methanesulfonyl Chloride–Dimethylaminopyridine

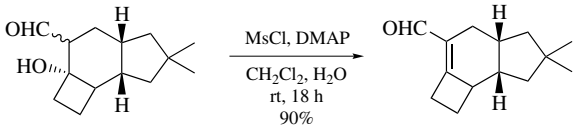


(MsCl)
[124-63-0] CH_3ClO_2S (MW 114.56)
InChI = 1/CH3ClO2S/c1-5(2,3)4/h1H3
InChIKey = QARBMVPHQWIHKH-UHFFFAOYAM
(DMAP)
[1122-58-3] $C_7H_{10}N_2$ (MW 122.19)
InChI = 1/C7H10N2/c1-9(2)7-3-5-8-6-4-7/h3-6H,1-2H3
InChIKey = VHYFNPMBLIVWCW-UHFFFAOYAL

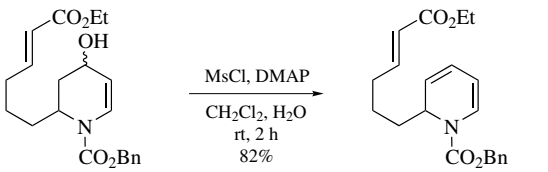
(conversion of alcohols to alkenes[1])

Alternate Name: Furukawa' reagent.
Physical Data: see methanesulfonyl chloride and 4-dimethylaminopyridine.
Preparative Method: MsCl (2.5 equiv), DMAP (1.25 equiv), H_2O (1 equiv), and CH_2Cl_2 are stirred at rt for 2–3 d.
Handling, Storage, and Precautions: effective even after 6 months; for handling the components, see methanesulfonyl chloride and 4-dimethylaminopyridine.

Conversion of Alcohols to Alkenes. Furukawa and coworkers found that treatment of alcohols with MsCl/DMAP/H_2O/CH_2Cl_2 (Furukawa' reagent) produces the dehydrated products in good yields (eq 1).[1] In the absence of water, the dehydrated products can still be formed, but in very poor yield. Some examples of secondary alcohols undergoing this elimination have also been reported (eq 2).[2]



(1)

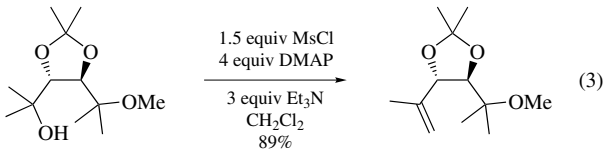


(2)

Yodav and co-workers reported that treatment of a variety of tertiary alcohols with methanesulfonyl chloride in the presence of DMAP and triethylamine produces the dehydrated products (eq 3).[3] Acid-sensitive functionalities are not affected by the reaction conditions.

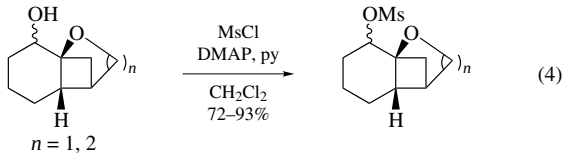
Mixtures of internal and terminal and *cis*- and *trans*-alkenes are formed in all cases. The reaction can be run at rt or below. For compounds with acid-sensitive groups, this method offers

advantages over the use of other reagents used to effect this transformation.



(3)

Mesylate Formation. Treatment of a secondary alcohol with methanesulfonyl chloride in the presence of DMAP yields the corresponding mesylate in good yield (eq 4).[4]



(4)

1. (a) Furukawa, J.; Morisaki, N.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S., *Chem. Pharm. Bull.* **1985**, *33*, 440. (b) Fieser, M.; Smith, J. G., *Fieser & Fieser* **1986**, *13*, 176.
2. (a) Comins, D. L.; Hong, H.; Salvador, J. M., *J. Org. Chem.* **1991**, *56*, 7197. (b) Comins, D. L.; Al-awar, R. S., *J. Org. Chem.* **1992**, *57*, 4098.
3. Yodav, J. S.; Mysorekar, S. V., *Synth. Commun.* **1989**, *19*, 1057.
4. Takahashi, M.; Uchino, T.; Ohno, K.; Tamura, Y., *J. Org. Chem.* **1983**, *48*, 4241.

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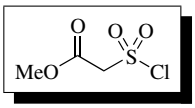
The Upjohn Company, Kalamazoo, MI, USA

Methoxycarbonylmethanesulfonyl Chloride

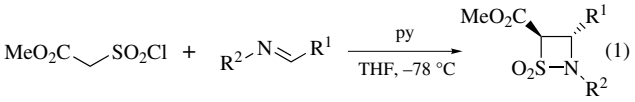


[56146-83-9] $C_3H_5ClO_4S$ (MW 172.60)
InChI = 1/C3H5ClO4S/c1-8-3(5)2-9(4,6)7/h2H2,1H3
InChIKey = YBIPZPBGAGTBGK-UHFFFAOYAS

(synthesis of sultam analogs of β-lactams;[3] synthesis of biologically active sulfonamides[4–6])

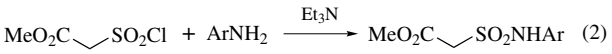
Physical Data: bp 98 °C/8 mm Hg; *d* 1.505 g cm^{-3}; fp >110 °C.
Solubility: sol C_6H_6, CH_2Cl_2, Et_2O.
Form Supplied in: colorless liquid.
Analysis of Reagent Purity: reagent purity may be determined by standard analytical techniques.
Preparative Methods: from chlorosulfonylacetyl chloride by reaction with 1 equiv of methanol;[1] may also be prepared by chlorination of sodium methoxycarbonylmethanesulfonate with phosphorus(V) chloride[2] or by direct chlorination of methyl thioglycolate.[3]
Purification: distillation under reduced pressure.
Handling, Storage, and Precautions: moisture sensitive; causes burns.

Synthesis of β-Sultams.[3] Formation of the β-sultam (eq 1) proceeds via addition of methoxycarbonylmethanesulfonyl chloride to a solution of the desired imine (1 equiv) and a tertiary amine base (1.5 equiv) at −78 °C. Best results are obtained using THF as the solvent and pyridine as the base. Yields are moderate to high. In general, the yields are higher when the R^1 substituent is aryl rather than alkyl.



(1)

Synthesis of Sulfonamides.[4–6] Sulfonamides are formed in moderate to good yields by the reaction of methoxycarbonylmethanesulfonyl chloride with the desired amine in the presence of triethylamine (eq 2). This reaction is usually carried out using arylamines, but can be extended to peptidic amines.[6]



(2)

1. Vieillefosse, R., *Bull. Soc. Chem. Fr.* **1947**, 351.
2. Oliver, J. E.; DeMilo, A. B., *Synthesis* **1975**, 321.
3. Szymonifka, M. J.; Heck, J. V., *Tetrahedron Lett.* **1989**, *30*, 2869.
4. Baltas, M.; Cazaux, L.; de Blic, A.; Gorrichon, L.; Tisnes, P.; Touati, A., *Bull. Soc. Chem. Fr.* **1988**, 79.
5. Musser, J. H.; Kreft, A. F.; Bender, R. W. H.; Kubrak, D. M.; Carlson, R. P.; Chang, J.; Hand, J. M., *J. Med. Chem.* **1989**, *32*, 1176.
6. Zecchini, G. P.; Paradisi, M. P.; Torrini, I.; Lucente, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G., *Tetrahedron Lett.* **1991**, *32*, 6779.

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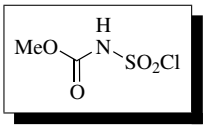
Methoxycarbonylsulfamoyl Chloride[1]



[36914-92-8] $C_2H_4ClNO_4S$ (MW 173.59)
InChI = 1/C2H4ClNO4S/c1-8-2(5)4-9(3,6)7/h1H3,(H,4,5)/f/h4H
InChIKey = DCGAEWHBJDXIAZ-JLSKMEETCB

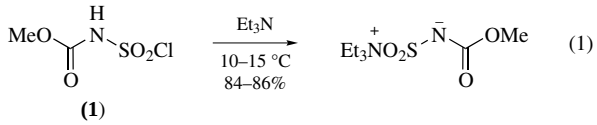
(precursor for the Burgess reagent;[1] regent for heterocyclic cycloaddition[6])

Physical Data: mp 70–74 °C.
Solubility: sol benzene, cyclohexane, THF, MeCN.
Form Supplied in: white crystalline solid.

Preparative Method: readily prepared in high yield from the reaction of chlorosulfonyl isocyanate and anhydrous methanol.[1]

Handling, Storage, and Precautions: is moisture sensitive and should be stored in a dark bottle, protected from light. Violent decomposition has been observed when the product is stored in a clear-glass container or when advertently exposed to sunlight.

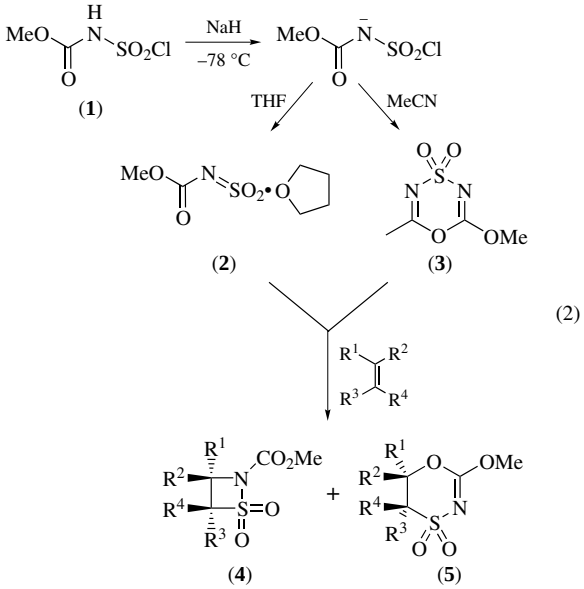
Formation of the Inner Salt of the Burgess Reagent. The reaction of anhydrous triethylamine with methoxycarbonylsulfamoyl chloride **(1)** in benzene produces the inner salt of methoxycarbonylsulfamoyl triethylammonium hydroxide (the Burgess reagent) (eq 1).[1] The Burgess reagent has been used in the formation of urethanes from primary alcohols; the urethanes are converted to primary amines upon hydrolysis.[1,2] The Burgess reagent has commonly been used in stereospecific *cis* elimination of secondary and tertiary alcohols to provide alkenes,[2,3] and in the synthesis of vinyltributyltin compounds.[4]



(1)

(**1**)

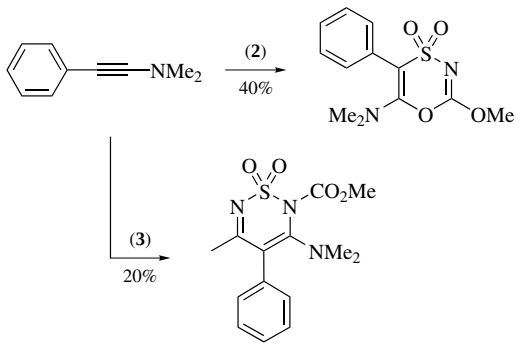
Cycloaddition Reactions. Deprotonation of reagent **(1)** with sodium hydride provides the salt form of reagent **(1)**, which undergoes cycloaddition with various alkenes. Decomposition of the salt form at 30 °C in THF yields the solvent complex of methyl *N*-sulfonylurethane, whereas reaction of the salt with acetonitrile, or other nitrile compounds, provides substituted 1,3,4,5-oxathiazines (eq 2). Both species are prone to cycloaddition reactions with alkenes (eq 2); however, the advantage of the latter species is the possibility of using higher reaction temperatures, thus enabling the formation of cycloadducts from otherwise unreactive alkenes.[5,6] The stereospecificity of the cycloaddition reaction has been investigated with a model substrate, *trans*-styrene-β-*d*, in both THF and acetonitrile. In both cases, cycloadducts **(4)** and **(5)** are formed in a ratio of 1:3 in 72% overall yield;[5] therefore, both [2 + 2] and [2 + 4] cycloadducts are formed with complete stereospecificity.



(**1**) (**2**) (**3**) (**4**) (**5**)

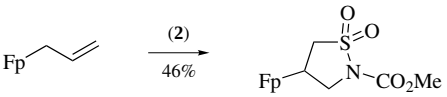
(2)

Intermediates **(2)** and **(3)** react with ynamines to form heterocycles (eq 3).[7] As with the cycloaddition reactions with alkenes, the nature of the product is dependent on whether species **(2)** or **3** is allowed to react with the ynamine.



(3)

Metal-assisted cycloadditions with intermediate **2** have been reported (eq 4).[8] These reactions are dominated by the metal functioning as an electron-donor center.



(4)

Fp = η^5-$C_5H_5Fe(CO)_2$

1. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M., *Org. Synth.* **1977**, *56*, 40.
2. Duncan, J. A.; Hendricks, R. T.; Kwong, K. S., *J. Am. Chem. Soc.* **1990**, *112*, 8433.
3. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A., *J. Org. Chem.* **1973**, *38*, 26.
4. Ratier, M.; Khatmi, D., *Synth. Commun.* **1989**, *19*, 285.
5. Burgess, E. M.; Williams, W. M., *J. Am. Chem. Soc.* **1972**, *94*, 4386.
6. Burgess, E. M.; Williams, W. M., *J. Org. Chem.* **1973**, *38*, 1249.
7. Kloek, J. A.; Leschinsky, K. L., *J. Org. Chem.* **1980**, *45*, 721.
8. Cutler, A.; Ehntholt, D.; Giering, W. P.; Lennon, P.; Raghu, S.; Rosan, A.; Rosenblum, M.; Tancrede, J.; Wells, D., *J. Am. Chem. Soc.* **1976**, *98*, 3495.

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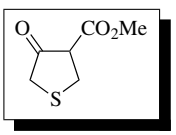
4-Methoxycarbonylthiolan-3-one



[2689-68-1] $C_6H_8O_3S$ (MW 160.21)

InChI = 1/C6H8O3S/c1-9-6(8)4-2-10-3-5(4)7/h4H,2-3H2,1H3

InChIKey = LEAKUJFYXNILRB-UHFFFAOYAF

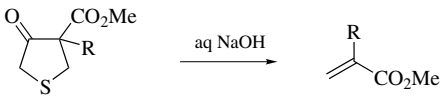
(building block for polynuclear heterocyclic compounds;[1,9] precursor of substituted thiophenes;[10–12] synthetic equivalent of α-acrylate anion[13,14])

Alternate Name: methyl 4-oxothiolane-3-carboxylate.

Physical Data: mp 37–38 °C;[15–17] bp 128.5 °C/20 mmHg,[15] 116–117 °C/9 mmHg,[18] 109 °C/4 mmHg;[15] IR (KBr[16] or CCl_4[17]), ^{1}H NMR,[16,17] MS,[17] and a study of the keto–enol equilibrium[18] have been reported.

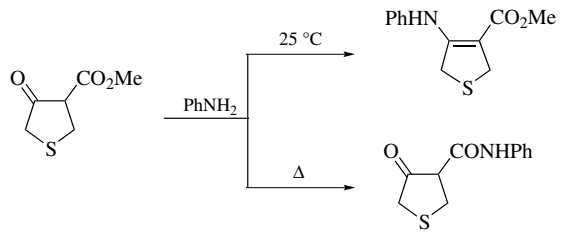
Preparative Methods: prepared by Dieckmann reaction of the Michael adduct of methyl thioglycolate and methyl acrylate. Careful choice of the reaction conditions (MeONa, toluene, 80–120 °C) and a suitable workup procedure are recommended in order to control the direction of the cyclization which, in principle, can produce both 3-oxo-2-carboxylate and 4-oxo-3-carboxylate isomers.[15–17,19] A more sophisticated method to accomplish a direction-controlled Dieckmann cyclization leading to exclusive formation of the target compound as the ethyl ester *[78647-31-1]* requires the less common ethoxycarbonylethyl thioethoxycarbonylmethyl sulfide as the starting material.[20]

α-Acrylate Anion Equivalent. Alkylation of 4-methoxycarbonylthiolan-3-one (**1**) with a variety of alkyl halides in the presence of potassium carbonate provides *C*-alkylated products in excellent yields. Their treatment with aqueous sodium hydroxide affords α-substituted acrylate esters through tandem Dieckmann–Michael retrograde reactions (eq 1).[13] This strategy has been successfully applied to the formal synthesis of integerrinecic acid.[14]



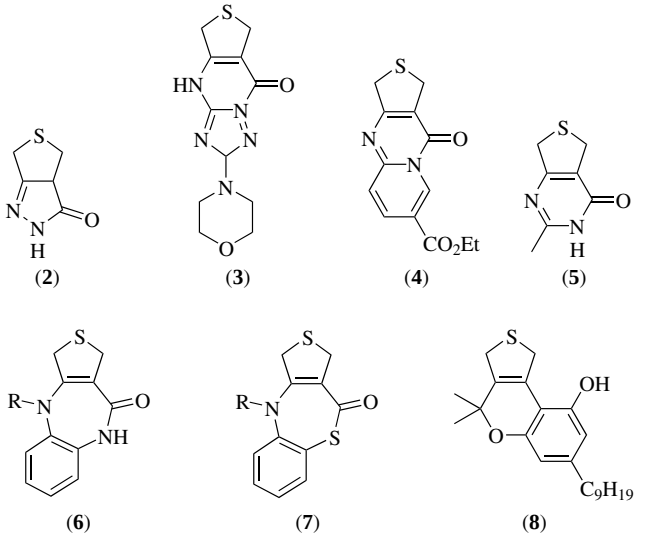
(1)

Building Block for Polynuclear Heterocyclic Compounds. Aniline can chemoselectively react with both the ester and ketone carbonyl groups of (**1**) affording an enamine or an amide, respectively, depending on the experimental conditions used (eq 2).[21]



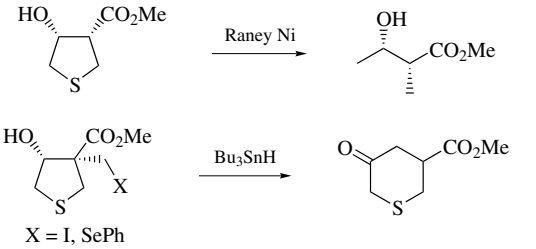
(2)

One of the most common synthetic approaches to the construction of heterocyclic compounds involves the reaction of β-keto esters with bifunctional nucleophiles. Thus a variety of reactions of (**1**) with different bifunctional heteronucleophiles, including hydrazine,[1] substituted aminotriazoles,[2] 2-aminopyridines,[3] *o*-phenylenediamines,[5–7] and *o*-aminothiophenol,[8] lead to polynuclear condensed thieno compounds (e.g. **2**–**8**) of potential medicinal interest featuring the pyrazolone, pyrimidinone, benzodiazepine, and benzothiazepine nuclei. Cannabinoid analogs can be prepared through cyclization of the condensation products of (**1**) with bifunctional oxygenated nucleophiles such as substituted resorcinols.[9]



Methyl (2*R*,3*S*)-2-Methyl-3-hydroxybutanoate.[22] This useful chiral building block, which is not easy to obtain with high optical purity by reduction of the corresponding open chain β-keto ester, can be conveniently prepared by diastereo- and enantioselective Baker's yeast reduction of (**1**), followed by Raney nickel promoted desulfurization (eq 3).

Ring Expansion. The *C*-alkylated products of (**1**) with diiodomethane[23] and chloromethyl phenyl selenide[24] undergo radical-promoted ring expansion on treatment with tributyltin hydride to give the expanded γ-keto ester in 64% yield (eq 4).



(3)

X = I, SePh

(4)

Related Reagents. 4-Cyanothiolan-3-one; Ethyl Acetoacetate; Ethyl Acrylate; Methyl 3-(Dimethylamino)propionate; Methyl 3-Hydroxypropionate.

1. Robba, M.; Boutamine, N., *Bull. Soc. Chem. Fr., Part 2* **1974**, 1629.
2. Esses-Reiter, K.; Reiter, J., *J. Heterocycl. Chem.* **1987**, *24*, 1503.
3. Connor, D. T.; Sorenson, R. J.; Tinney, F. J.; Cetenko, W. A. Kerbleski, J. J., *J. Heterocycl. Chem.* **1982**, *19*, 1185.
4. Tomé, A. C.; O'Neill, P. M.; Storr, R. C.; Cavaleiro, J. A. S., *Synlett* **1993**, 397.
5. Press, J. B.; Hofmann, C. M.; Eudy, N. H.; Fanshawe, W. J.; Day, I. P.; Greenblatt, E. N.; Safir, S. R., *J. Med. Chem.* **1979**, *22*, 725.
6. Chakrabarti, J. K.; Fairhurst, J.; Gutteridge, N. J. A.; Horsman, L.; Pullar, I. A.; Smith, C. W.; Steggles, D. J.; Tupper, D. E.; Wright, F. C., *J. Med. Chem.* **1980**, *23*, 884.
7. (a) Hromatka, O.; Binder, D.; Eichinger, K., *Monatsh. Chem.* **1974**, *105*, 1164. (b) Hromatka, O.; Binder, D.; Eichinger, K., *Monatsh. Chem.* **1975**, *106*, 375, 555.

8. Press, J. B.; Eudy, N. H.; Safir, S. R., *J. Org. Chem.* **1980**, *45*, 497.
9. Razdan, R. K.; Terris, B. Z.; Handrick, G. R.; Dalzell, H. C.; Pars, H. G.; Howes, J. F.; Plotnikoff, N.; Dodge, P.; Dren, A.; Kyncl, J.; Shoer, L.; Thompson, W. R., *J. Med. Chem.* **1976**, *19*, 549.
10. Press, J. B.; Hofmann, C. M.; Safir, S. R., *J. Org. Chem.* **1979**, *44*, 3292.
11. Banks, M. R.; Barker, J. M.; Huddleston, P. R., *J. Chem. Res. (S)* **1984**, 27.
12. Struharik, M.; Hrnciar, P., *Chem. Abstr.* **1987**, *107*, 58 771w.
13. Baraldi, P. G.; Barco, A.; Benetti, S.; Moroder, F.; Pollini, G. P.; Simoni, D.; Zanirato, V., *J. Chem. Soc., Chem. Commun.* **1982**, 1265.
14. Baraldi, P. G.; Guarneri, M.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S., *J. Chem. Soc., Perkin Trans. 1* **1984**, 2501.
15. Woodward, R. B.; Eastman, R. H., *J. Am. Chem. Soc.* **1946**, *68*, 2229.
16. Rossy, P. A.; Hoffmann, W.; Müller, N., *J. Org. Chem.* **1980**, *45*, 617.
17. Liu, H.-J.; Ngooi, T. K., *Can. J. Chem.* **1982**, *60*, 437.
18. Duus, F., *Tetrahedron* **1981**, *37*, 2633.
19. Hromatka, O.; Binder, D.; Eichinger, K., *Monatsh. Chem.* **1973**, *104*, 1348.
20. Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K., *Tetrahedron Lett.* **1981**, *22*, 1353.
21. Jaunin, R., *Helv. Chim. Acta* **1980**, *63*, 1542.
22. Hoffmann, R. W.; Helbig, W.; Ladner, W., *Tetrahedron Lett.* **1982**, *23*, 3479.
23. Dowd, P.; Choi, S.-C., *Tetrahedron Lett.* **1989**, *30*, 6129.
24. Dowd, P.; Choi, S.-C., *Tetrahedron* **1991**, *47*, 4847.

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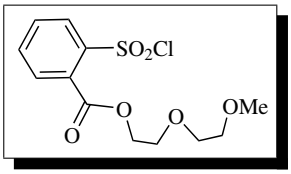
2-(2-Methoxyethoxy)-ethyl 2-(Chlorosulfonyl)-benzoate



[866942-11-2] $C_{12}H_{15}ClO_6S$ (MW 322.76)

InChI = 1/C12H15ClO6S/c1-17-6-7-18-8-9-19-12(14)10-4-2-3-5-11(10)20(13,15)16/h2-5H,6-9H2,1H3

InChIKey = TVQUWKKLSJIKOI-UHFFFAOYAP

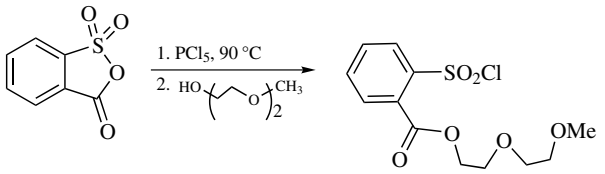
(reagent used to form a leaving group that is selectively reactive toward a variety of reagents including Ti(IV) halides and azides, metal halide salts, and positron-emitting metal fluorides)

Solubility: soluble in methylene chloride, ethyl ether, alcohol, and most other organic solvents; not soluble in H_2O.

Form Supplied in: colorless oil; not currently commercially available.

Handling, Storage, and Precautions: protection from moisture and heat significantly extends the shelf life of this rather stable reagent. With refrigeration, this reagent can be stored for 6 months or more with no decomposition. Although its toxicity has not been studied, this sulfonyl chloride reagent is likely to be harmful if swallowed or absorbed through the skin.

Reagent Preparation. Despite the wide variety of available leaving groups, there is still a need to improve their performance in terms of selectivity, reaction rates, scalability, environmental compatibility, atom economy, and other parameters.[1] Leaving groups containing chelating units capable of stabilizing the transition state of a nucleophilic reaction have been shown to dramatically enhance reaction rates relative to traditional leaving groups such as tosylates.[2] Such nucleofuges have been termed nucleophile-assisting leaving groups (NALGs).[1] The present reagent 2-(2-methoxyethoxy)-ethyl 2-(chlorosulfonyl) benzoate[3] reacts with alcohols (eq 2) to produce compounds that contain a chelating leaving group. It is prepared using one of the following two procedures (eq 1).



(1)

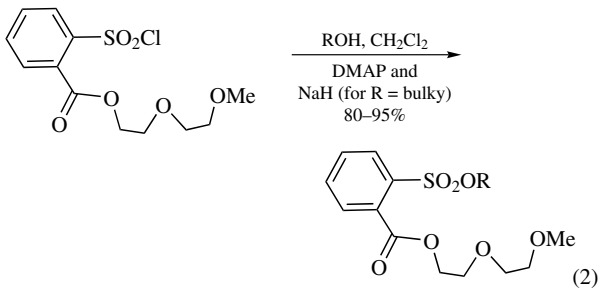
Procedure 1: A mixture of sulfobenzoic acid anhydride (1.0 equiv) and phosphorus pentachloride (2.0 equiv) was heated at 90 °C for 6 h. The oil was allowed to cool, dissolved in ether, and rinsed with ice water to remove unreacted phosphorus pentachloride. The solvent was evaporated in vacuo. The crude oil (1.0 equiv) was then dissolved in excess 2-(2-methoxyethoxy) ethanol (5.0 equiv) and heated to 60 °C for 30 h. The reaction mixture was purified by flash chromatography by eluting with a hexane/acetone (85:15 v/v) to yield the sulfonyl chloride as a colorless oil (95% yield).

Procedure 2 (alternative): A mixture of sulfobenzoic acid anhydride (1.0 equiv) and 2-(2-methoxyethoxy) ethanol (1.5 equiv) was stirred at room temperature for 1 h. The reaction mixture was allowed to stir overnight at room temperature after the addition of phosphorus pentachloride (2.0 equiv). The reaction mixture was dissolved in ether and rinsed with ice water to remove unreacted phosphorus pentachloride. The solvent was evaporated in vacuo. The crude oil was purified by flash chromatography by eluting with a hexane/acetone (85:15 v/v) to yield the sulfonyl chloride as a colorless oil (90% yield). Although affording slightly lower yields, procedure 2 calls for fewer equivalents of the ether–alcohol that is to become the chelating side arm. This would be advantageous for the synthesis of related NALGs containing more costly side units.

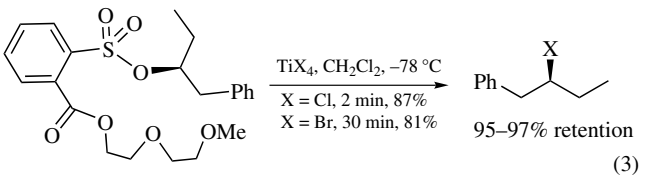
Sulfonate ester NALGs are prepared via a DMAP-catalyzed addition of alcohols to 2-(2-methoxyethoxy)-ethyl 2-(chlorosulfonyl) benzoate (eq 2). For more hindered cases, the alcohol was first converted to the sodium alkoxide using NaH followed by the addition of 2-(2-methoxyethoxy)-ethyl 2-(chlorosulfonyl) benzoate. For the most hindered alcohols, both DMAP and NaH were used to give the sulfonate product (NALG) in good yields (80–95%) with shorter reaction times. In all cases, sulfonate NALGs were exceptionally stable to aqueous workup and silica gel chromatography.[2]

Stereoretentive Halogenation of Secondary Alkyl Substrates. A stereoretentive method to convert NALG sulfonates, derived from the reaction of 2-(2-methoxyethoxy)-ethyl 2-(chloro sulfonyl) with secondary alcohols, to the corresponding

chlorides using $TiCl_4$ has been reported.[4] This is particularly significant since, if neighboring group participation[5] and metal-catalyzed allylic substitution[6] are excluded, there are exceedingly few reports of nucleophilic displacement reactions on saturated carbon leading to products with a high degree of retention of configuration.[7] In methylene chloride, this chlorination reaction was completed within 5 min at −78 °C leading to high yields for a broad range of secondary substrates (eq 3). Analogous bromination results were obtained with $TiBr_4$ (eq 3).[8] This stereoretentive bromination reaction has been recently used in a natural product total synthesis.[9] Importantly, these halogenation reactions proceed with complete retention of configuration likely via a front-side S_Ni-type mechanism.

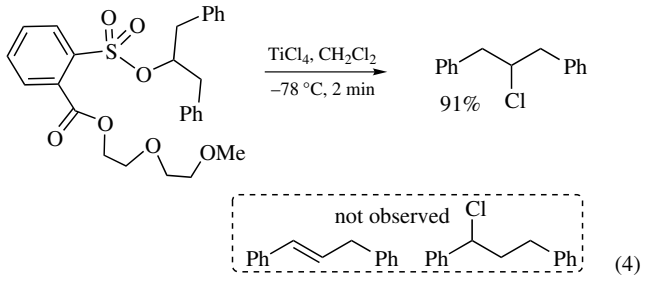


(2)



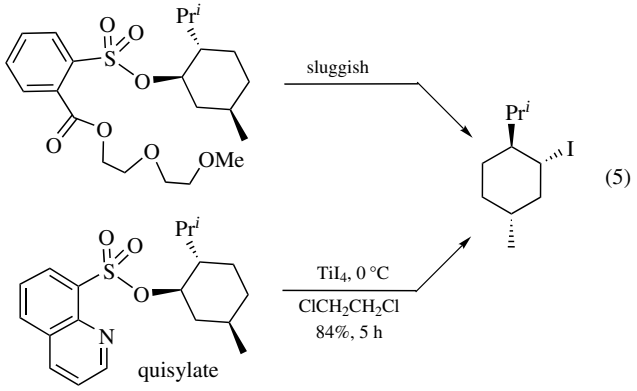
(3)

These halogenations are also highly resistant to an ionization pathway as indicated by the lack of side product formation in the conversion of the NALG of 1,3-diphenyl-2-propanol to the corresponding chloride and bromide products (eq 4). To our knowledge, 1,3-diphenyl-2-chloropropane has only been prepared by radical chlorodecarboxylation methods.[10] Overall, the NALG-TiX_4 method offers an important alternative to existing techniques for the synthesis of secondary alkyl halides especially where retention of configuration is required.



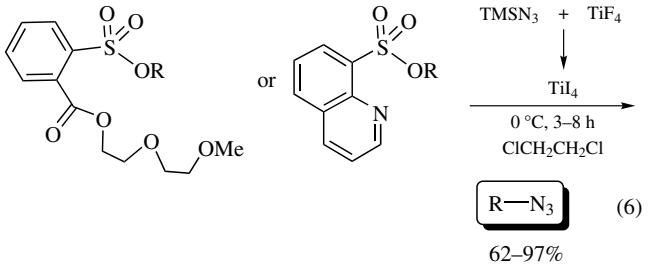
(4)

In some cases, bromination and especially iodination of NALGs derived from 2-(2-methoxyethoxy) ethyl 2-(chlorosulfonyl) benzoate may be excessively slow. Improved reaction rates were achieved with a new leaving group based on the commercially available 8-quinoline sulfonyl chloride (quisyl group). Thus, menthyl sulfonate ester was converted into the corresponding iodo-product in 84% yield with complete retention of configuration using TiI_4 at 0 °C in 1,2-dichloroethane (eq 5).[8] Under the same conditions, 1,3-diphenyl-2-propanyl quisylate was converted into the corresponding iodide in 90% yield in 5 h (not shown).



(5)

Stereoretentive Azidation. Azides are typically prepared from substitution of alkyl halides and tosylates with sodium azide with inversion of configuration.[11] A stereoretentive approach has been developed based on the reaction of $Ti(N_3)_4$ with sulfonate NALGs particularly quisylates. Yields for this transformation are generally between 60 and 97% for acyclic and cyclic substrates, including cholesteryl and substituted cycloalkanes.[8] This azidation reaction is less successful with substrates poorly able to stabilize partial positive charge at the substitution site (such as aryl sulfonates of α-hydroxyesters or primary alcohols). To our knowledge, this reaction is the first reported stereoretentive azidation of alcohol derivatives not involving a double inversion technique (eq 6).

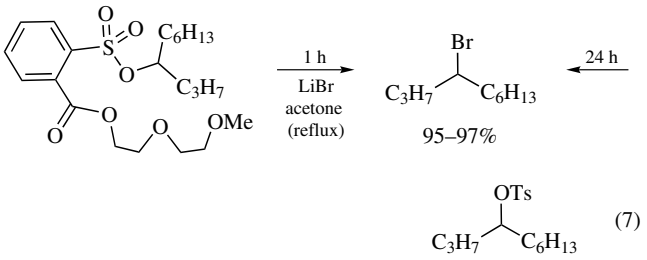


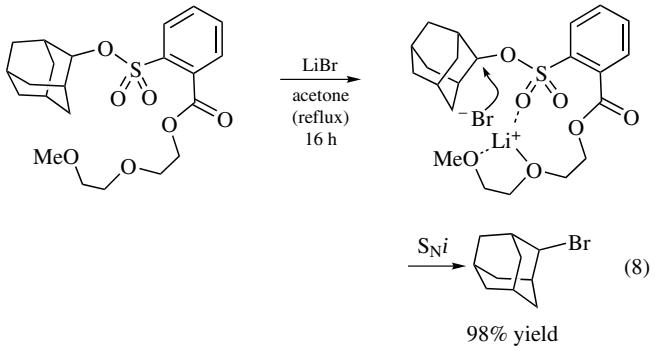
(6)

Reaction with Metal Halides. The sulfonate esters of 2-(2-methoxyethoxy)-ethyl 2-(chlorosulfonyl) benzoate exhibit unique reactivities in substitution reactions with metal halides. These reactions proceeded at substantially greater rates than electronically similar sulfonates such as tosylates.[2] The reaction of substrates containing NALGs derived from 2-(2-methoxyethoxy)-ethyl 2-(chlorosulfonyl) benzoate is significantly faster with nucleophilic reagents containing metal salts especially lithium. For example, LiBr reacts with these NALGs to give alkyl bromide products at over 20 times the rate of the corresponding tosylates (eq 7). Indeed, in most cases these NALG substrates are as reactive as triflates toward substitution but significantly easier to handle and purify and generally lead to fewer side products.[4]

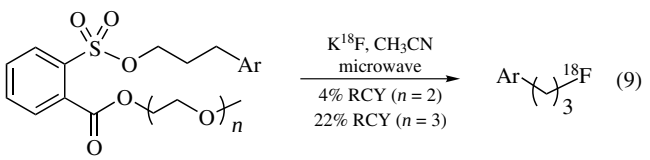
For the reaction of LiBr with adamantyl-NALG, where back-side attack is precluded, a quantitative yield with 2-bromo-adamantane was obtained whereas the corresponding tosylate

gave no product even after extended reaction times (eq 8). The 2-adamantyl triflate analog also failed to give the corresponding bromide with attack occurring exclusively at the triflate sulfonyl, liberating 2-admantanol as the main product. This example appears to support a front-side S_N1 or a concerted mechanism (S_Ni type).

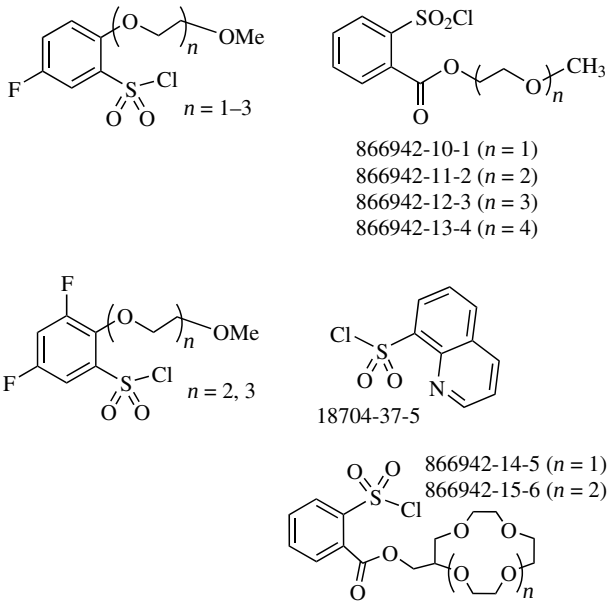




Nucleophilic Radiofluorination. This enhanced reaction of NALGs derived from 2-(2-methoxyethoxy)-ethyl 2-(chlorosulfonyl) benzoate has also been used to introduce positron-emitting fluoride into substrates.[12] These reactions often performed with $K^{18}F$ produced from a cyclotron have traditionally required a phase-transfer agent such as K.2.2.2 (Kryptofix, a commercially available cryptand favoring potassium binding). However, a nontrivial purification is required to remove the Kryptofix additive. Radioactive nuclei such as fluoride (half-life of 110 min) must be introduced quickly with minimal purification to be useful as a medical imaging agent. With a primary substrate containing a NALG derived from 2-(2-methoxyethoxy)-ethyl 2-(chlorosulfonyl) benzoate, radioactive fluoride is poorly incorporated (eq 9, n = 2). However, an NALG with an additional ethylene oxide unit in the chelating sidearm (n = 3) led to a 22% radiochemical yield (RCY) with $K^{18}F$ under microwave conditions (eq 9). This is over three times the yield achieved using the tosylate leaving group under identical conditions and is the highest reported radiochemical yield of a primary substrate using $K^{18}F$ unassisted by a phase-transfer catalyst.[12]



Related Reagents.



1. Lepore, S. D.; Mondal, D., *Tetrahedron* **2007**, *63*, 5103.
2. Lepore, S. D.; Bhunia, A. K.; Cohn, P. C., *J. Org. Chem.* **2005**, *70*, 8117.
3. Lepore, S. D., Nucleophile assisting leaving groups. *PCT Int. Appl.* (2006).
4. Lepore, S. D.; Bhunia, A. K.; Mondal, D.; Cohn, P. C.; Lefkowitz, C., *J. Org. Chem.* **2006**, *71*, 3285.
5. Some recent examples include (a) Liu, L. X.; Huang, P. Q., *Tetrahedron: Asymmetry* **2007**, *17*, 3265. (b) Concellon, J. M.; Bernad, P. L.; Suarez, J. R.; Garcia-Granda, S.; Diaz, M. R., *J. Org. Chem.* **2005**, *70*, 9411. (c) De Paolis, M.; Blankenstein, J.; Bois-Choussy, M.; Zhu, J., *Org. Lett.* **2002**, *4*, 1235.
6. Some recent examples include (a) Lloyd-Jones, G. C.; Krska, S. W.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Reamer, R. A., *J. Am. Chem. Soc.* **2004**, *126*, 702. (b) Sato, Y.; Yoshino, T.; Mori, M., *Org. Lett.* **2003**, *5*, 31.
7. Some examples include (a) Lee, I.; Kim, H. Y.; Kang, H. K.; Lee, H. W., *J. Org. Chem.* **1988**, *53*, 2678. (b) Gasteiger, J.; Kaufmann, K.; Herzig, C.; Bentley, T. W., *Tetrahedron Lett.* **1985**, *26*, 4337. (c) Cayzergues, P.; Georgoulis, C.; Ville, G. J., *Chem. Res. Synopses* **1978**, *9*, 325.
8. Lepore, S. D.; Mondal, D.; Li, S. Y.; Bhunia, A. K., *Angew. Chem., Int. Ed.* **2008**, *47*, 7511.
9. Park, J.; Kim, B.; Kim, H.; Kim, S.; Kim, D., *Angew. Chem., Int. Ed.* **2007**, *46*, 4726.
10. (a) Okada, K.; Okamoto, K.; Oda, M., *J. Chem. Soc., Chem. Commun.* **1989**, *21*, 1636. (b) Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Tetrahedron* **1985**, *41*, 3901.
11. For general reviews on azides, see (a) Scriven, E. F. V.; Turnbull, K., *Chem. Rev.* **1988**, *88*, 297. (b) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V., *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
12. Lu, S.-Y.; Lepore, S. D.; Li, S. Y.; Mondal, D.; Bhunia, A. K.; Pike, V. W., *J. Org. Chem.* **2008**, (submitted).

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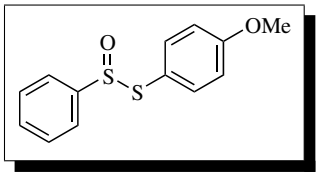
Methoxyphenyl Benzenethiosulfinate



[26974-26-5] $C_{13}H_{12}O_2S_2$ (MW 264.36)

InChI = 1/C13H12O2S2/c1-15-11-7-9-12(10-8-11)16-17(14)13-5-3-2-4-6-13/h2-10H,1H3

InChIKey = AUBYFXQFOLVHFE-UHFFFAOYAP

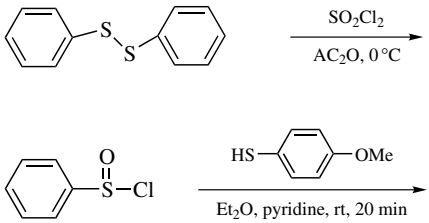
(reagent used for the activation of thioglycosides[1])

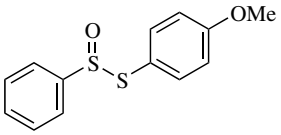
Physical Data: pale yellow crystals, mp 77–78 °C; mass spectrum.[2]

Solubility: soluble in most organic solvents.

Analysis of Reagent Purity: ^1H and ^{13}C NMR.[1]

Preparative Methods: the reagent is prepared from benzenesulfinyl chloride and *p*-methoxythiophenol (eq 1).[1]





(1)

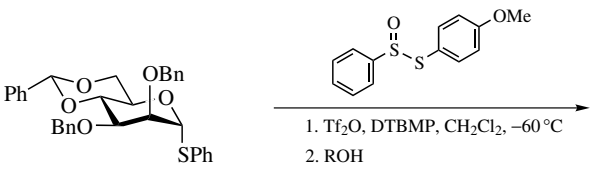
Purity: recrystallization from ether-petroleum ether (bp 40– 60 °C).

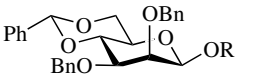
Handling, Storage, and Precautions: crystalline, odorless, and stable on the laboratory bench at room temperature when stored in standard amber bottles.

***S*-(4-Methoxyphenyl) Benzenethiosulfinate (MPBT)/Trifluoromethanesulfonic Anhydride (Tf_2O): A Powerful Activating System for Thioglycosides and for the Formation of Glycosidic Linkages.** The combination of MPBT with Tf_2O forms a powerful, metal free, thiophile that can readily activate thioglycosides via glycosyl triflates in a matter of minutes at −60 °C in dichloromethane, in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).[2] The glycosyl triflates are rapidly and cleanly converted to glycosides upon treatment with alcohols. This method has allowed access to β-mannosides (eq 2) and α-glucosides in good yield and selectivity.

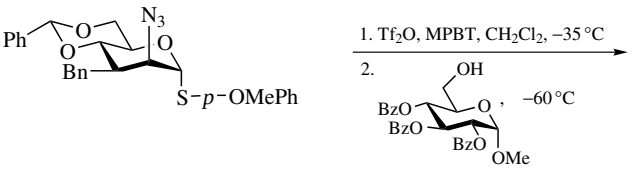
Generally, the combination of MPBT/Tf_2O cannot activate disarmed thioglycosides at low temperature, but in some case when the more electron-donating *p*-methoxyphenylthio group is used as the anomeric function, good yield and stereoselectivity can still be achieved (eq 3).[3]

This limitation of activation has been overcome by the combination of 1-benzenesulfinyl piperidine (BSP) and Tf_2O.[4]





(2)

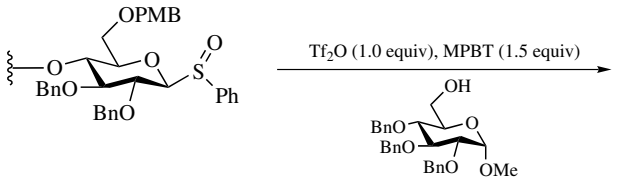


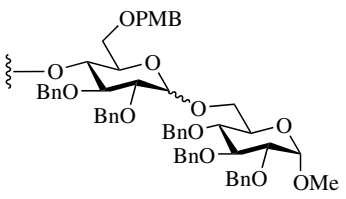
yield: 87%

ratio: α/β = 1/4

(3)

Other Reactions. In some glycosylation reactons, stoichiometric amount of *S*-(4-methoxyphenyl)benzenethiosulfinate is reported to function as an acid scavenger to avoid the undesired removal of PMB protection that prevailed on activation by Tf_2O alone (eq 4).[5]





yield: 58%

ratio: α/β = 1/4

(4)

It is reported that the mixture of disulfide and thiosulfinate, such as *S*-(4-methoxyphenyl) benzenethiosulfinate, can be used as an antioxdant for the retardation of autoxidation of olefins.[6]

Related Reagents. 1-Benzenesulfinyl Piperidine; Dimethyl (Methylthio)sulfonium Tetrafluoroborate; *N*-Iodosuccinimide; Diphenyl Sulfoxide.

1. Crich, D.; Smith, M., *Org. Lett.* **2000**, *2*, 4067.
2. Kozuka, S.; Takahashi, H.; Oae, S., *Bull. Chem. Soc. Jpn.* **1970**, *43*, 129.
3. Litjens, R. E. J. N.; Leeuwenburgh, M. A.; Marel, G. A.; Boom, J. H., *Tetrahedron Lett.* **2001**, *42*, 8693.
4. Crich, D.; Smith, M., *J. Am. Chem. Soc.* **2001**, *123*, 9015.
5. Ferguson, J.; Marzabadi, C., *Tetrahedron Lett.* **2003**, *44*, 3573.
6. Cole, E. R., *Phosohorus Sulfur Silicon* **1991**, *63*, 147.

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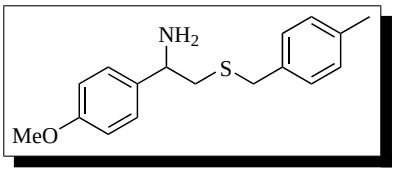
1-(4-Methoxyphenyl)-2-(4′-methylbenzylthio)ethylamine[1]



[403739-55-9] $C_{17}H_{21}NOS$ (MW 287.42)

InChI = 1/C17H21NOS/c1-13-3-5-14(6-4-13)11-20-12-17(18)15-7-9-16(19-2)10-8-15/h3-10,17H,11-12,18H2,1-2H3

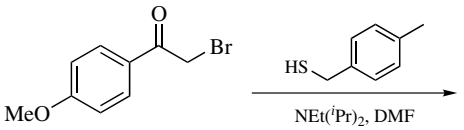
InChIKey = MTYGTBRKASPSQE-UHFFFAOYAA

(auxiliary used in the native chemical ligation of peptides and proteins)

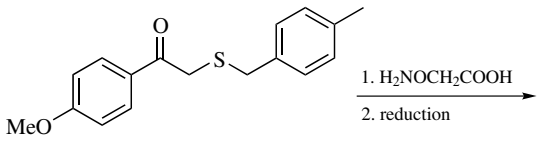
Form Supplied in: not commercially available.

Preparative Methods: 1-(4-methoxyphenyl)-2-(4′-methylbenzylthio)ethylamine **3** was prepared in three steps from *p*-methoxy bromoacetophenone **1**. Reaction with a suitable resin-bound bromoacetyl peptide,[2] followed by *S*-deprotection gives the peptide **4**, derivatized with the N^{α}-(1-(4-methoxyphenyl)-2-mercaptoethyl) auxiliary (eq 1).

The title compound **3** has been used in native chemical ligation (NCL) for the chemical synthesis of proteins.[3–7] NCL selectively couples unprotected peptide segments to form larger polypeptides and proteins (up to ~300 amino acid residues). The reaction occurs in aqueous systems at pH 7.0–7.2, and is chemoselective between an *N*-terminal cysteine peptide and a thioester. The thioester undergoes dynamic thiol exchange with the cysteine functionality (usually catalyzed by an aryl or alkyl thiol), which then rearranges "irreversibly" through a five-membered transition state to the native amide bond (eq 2). The chemoselectivity of this reaction arises from: 1. the protonation of other nucleophiles in the peptide at pH 7 (disfavoring undesirable acylation, *e.g.*, at the γ-amino group of lysine residues); 2. the facile thioester exchange between COSR and the cysteine SH; and 3. the rapid rearrangement of the resulting α-amino thioester. This method has been combined with molecular biology techniques such as protein design and expression to expand the scope of proteins that can be synthesized and modified.[8,9]



1



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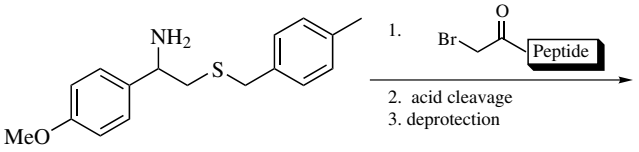
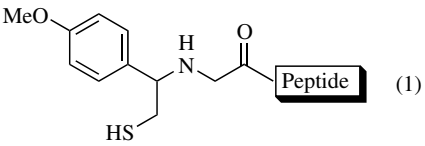
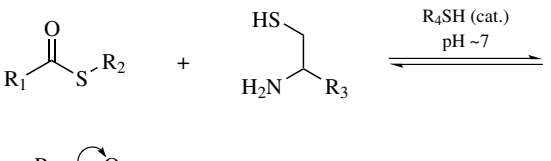


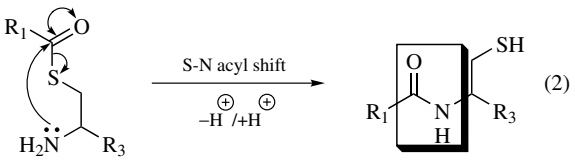
3



(1)

4





(2)

native amide bond

One of the major limitations of the thioester-cysteine mediated ligation is the necessity for cysteine residues in the target molecule. Similar ligation strategies have been developed that exploit alternative acyl shifts between other functionality, *e.g.*, the imidazole of histidine residues.[5] However, the most general of these alternative strategies involves the use of removable ligation auxiliaries such as **3**, which enable disconnection at a glycine residue. These auxiliaries provide an aryl or alkyl thiol α- or β- to an amine for thioester exchange and rearrangement to the amide. The use of auxiliary **3** offers several advantages over earlier systems, including rapid ligation rates and ease of removal postligation. The effectiveness of this auxiliary was first assessed using a model peptide of sequence N^{α}-(Aux)GlySerTyrArgPheLeu.[1] This was successfully ligated with a number of thioester peptides, as illustrated below (eq 3), (Table 1), with post-ligation auxiliary removal achieved using either 95% HF/5% *p*-cresol or trifluoroacetic acid (TFA)/bromotrimethyl silane (TMSBr).[10,11]

Use of 1-(4-Methoxyphenyl)-2-(4′-methylbenzylthio)ethylamine. Auxiliary **3** has been applied to the formation of cyclic peptides[12] and in the synthesis of cytochrome b562.[13]

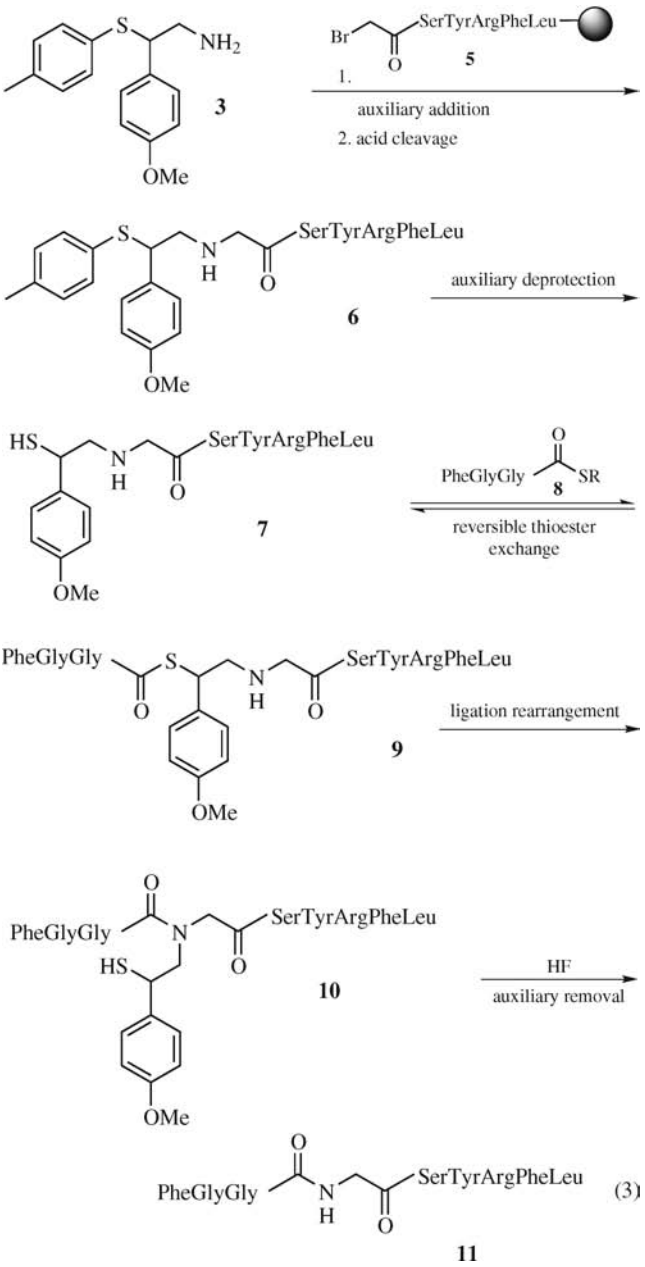


Table 1 Ligation studies with auxiliary **3**

Peptide-αCO-SR	Reaction Time (h)[a]	Ligation Yield(%)[b]	Auxiliary Removal
Phe-Gly-Gly	16	>98	HF
Mouse Larc 1-31 (Ala)	40	92	HF
MCP1 1–35 (Lys)	40	76	TFA/TMSBr

[a]Ligation conditions: 5 mM N^{α}-(Aux) peptide in 6 M guanidinium phosphate buffer pH 7, 25 °C, 2% thiophenol

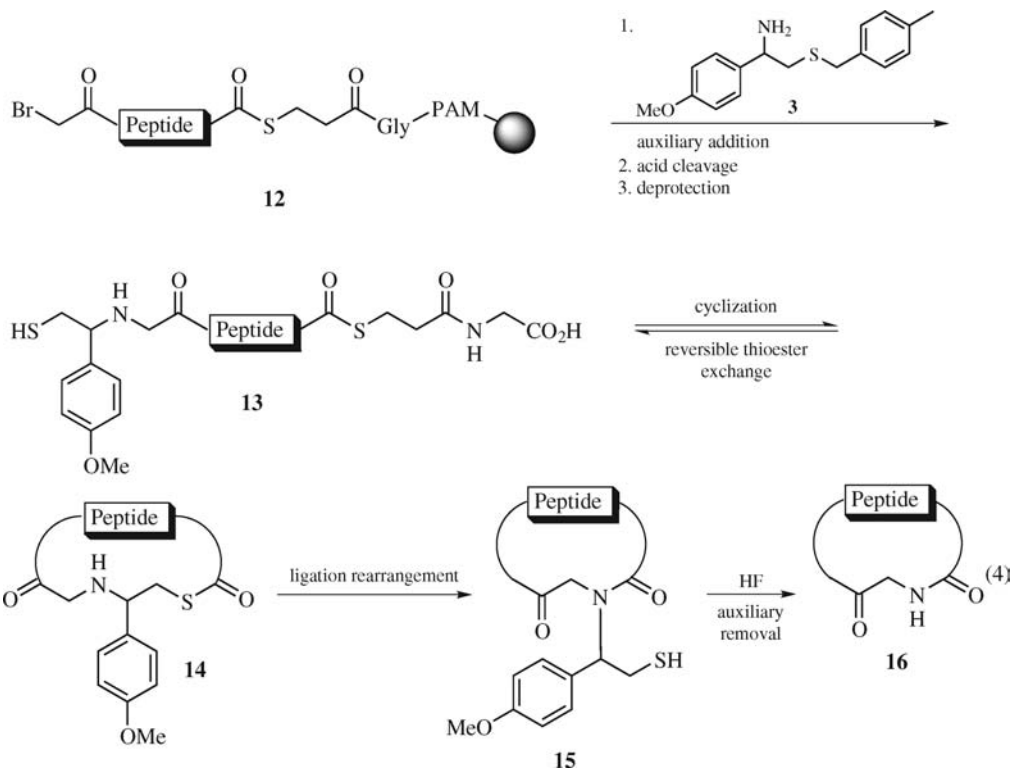
[b]Based on consumption of the N^{α}-(Aux) peptide. Thioester peptides were used in 1.5-fold excess.

Cyclic Peptides.[12] Cyclic peptides are known to possess greater metabolic stability, biological activity, and receptor selectivity than their linear counterparts.[14] Consequently, much effort has been directed towards their synthesis, via cyclic lactam or disulfide bridge formation for example.[15–18] However, these methods suffer from problems such as the necessity of protecting group manipulation and the use of organic solvents in lactam formation and the metabolic instability of disulfide bonds. Classical NCL, making use of cysteine residues, has recently been applied to surmount these problems, resulting in the synthesis of a variety of cyclic peptides.[19] Earlier incarnations of NCL auxiliaries,[20] albeit with the reported problems associated with these reagents, have also been employed in the synthesis of cyclic peptides. The 1-(4-methoxyphenyl)-2-(4′-methylbenzylthio)ethylamine auxiliary **3** has been used to form an 11-amino acid cyclic peptide, the linear analog of which is derived from an anti HIV-1 lead compound. The peptide is amenable neither to Xxx-Cys nor Gly-Gly cyclative coupling, necessitating the use of the auxiliary **3**. Linear peptide synthesis was achieved using standard solid phase peptide synthesis techniques with a thioester linkage to the solid support, with the auxiliary attached to the *N*-terminus via the bromide as discussed above (eq 4). To effect cyclization, **9** was dissolved in freshly degassed sodium phosphate (0.2 M) pH 7.5, thiophenol was added (0.1% v/v) and the pH adjusted to 7.4. The reaction was complete within 2 h (by RP-HPLC) and purification was achieved with preparative RP-HPLC (C_{18} column, gradient 20–90% B over 35 min; A: 0.1% aq TFA, B: acetonitrile + 0.1% TFA). The auxiliary was removed using 95% HF, 5% *p*-cresol at 0 °C for 1 h to give the cyclic peptide in 22.5% yield from the linear peptide.

Cytochrome b562 Synthesis.[13] The total chemical synthesis of cytochrome b562, and that of an axial ligand analog, [SeMet[7]]cyt b562, was achieved using native chemical ligation of two unprotected peptide segments via the 1-(4-methoxyphenyl)-2-(4′-methylbenzylthio)ethylamine auxiliary approach.

Automated solid phase peptide synthesis was used to generate three peptide fragments, with the auxiliary introduced as an on-resin modification of the amino terminus of peptide cyt b562 (64-106) [G(Aux)FDILVGQIDDALKLANEGKVK-EAQAAAEQL KTTRNAYHQKYR]. Two further peptide sequences were then synthesised, representing cyt b562(1-63) wild-type and [SeMet[7]] cyt b562(1-63), using a thioester generating resin to form the peptides required for native chemical ligation [ADLEDN*X*ETLNDN LKVIEKADNAAQVKDALTKMRAAALDAQKATPPKLEDK SPDSPEMKDFRH(COSR), where *X* = Met or SeMet].

This synthesis exemplifies the specific advantages provided by the use of ligation auxiliaries. Analysis of the protein structure predicted that modification of the sequence to include Cys as a replacement for Gly[64] would create unfavorable steric interactions and that the resulting protein would not fold. Attempts to use D-Cys in place of L-Cys (thus circumventing the steric problems) still disrupted folding of the protein (presumably due to destabilization of the helix by the D-amino acid). Thus the ligation auxiliary **3** was employed, allowing ligation of the peptides while still leaving the native Gly at position 64. Native chemical ligation was conducted at room temperature, with peptides dissolved in 6 M guanidine.HCl buffered at pH 7 with 0.3 M sodium phosphate, with 0.5–2% thiophenol as a catalyst. Following purification by semipreparative HPLC, treatment with HF for 1 h at 0 °C cleaved the auxiliary, providing the native polypeptide.



Protein folding was then accomplished using a heme solution, giving the native protein cyt b562 and [SeMet[7]]cyt b562, as determined by electrospray MS, CD spectra, and cyclic voltammetry.

Potential Use of Ligation Auxiliaries Outside of Peptide and Protein Synthesis. Auxiliaries such as **3** have greatly improved the generality of native chemical ligation. They also have the potential to expand the scope of chemical ligation beyond protein and peptide synthesis, as in the ligation of fluorophores and affinity tags to biomolecules via cysteine.[21,22] The use of auxiliary-mediated ligation could further generalize the conjugation of non-peptide molecules in a mild, chemoselective fashion. This chemistry provides a tool for the synthetic chemist, and may prove particularly useful as a method for the selective formation of amide bonds in the presence of other amines with minimal use of protecting groups.

The majority of these auxiliaries have not yet found widespread application in the synthesis of complex peptides, despite the fact that cysteine is a relatively rare amino acid, constituting

Related Reagents. *S*-(4-Methylbenzyl)-2-(aminooxy)ethanethiol: This auxiliary, which is easily removed following ligation by N-O bond cleavage with Zn in acetic acid, suffers from a slower cyclization step due the six-membered transition state.[20]

S-[(3-Carboxy-4-nitrophenyl)thio]-2-aminoethanethiol: The five-membered transition state permitted by this auxiliary allows rapid ligation rearrangement, offering a solution to the problem of the above reagent, however, this auxiliary is no longer removable after ligation.[20]

2-Mercaptobenzaldehyde: Condensation of this auxiliary with a terminal amine gives an acid stable benzyl amine, but leaves an acid labile benzylamide after cyclization. This method again suffers due to a six-membered transition state.[24]

4,5-Dimethoxy-2-tritylthiobenzylamine,[25] 4,5,6-Trimethoxy-(2-4′-methylbenzylthio)-benzylamine:[26] These groups are also reductively coupled to terminal amines, with the methoxy groups serving to increase aryl ring electron density and hence ligation efficiency and acid lability.

1-(2-Nitrophenyl)-2-tritylthioethylamine: Addition of the nitro group to the benzylamine allows this reagent to take advantage of the rapid ligation rates of **3**; post ligation removal is achieved by simple photolysis.[27]

1-Hydroxyl-1-(4-methoxyphenyl)-2-*tert*-butylthioethane: This intermediate, formed from in situ from the corresponding alcohol, allows the attachment of the 2-mercaptobenzylamine-type auxiliary to a terminal amine, thereby extending the number of amino acids to which this moiety may be coupled.[28]

1. (a) Botti, P.; Carrasco, M. R.; Kent, S. B. H., *Tetrahedron Lett.* **2001**, *42*, 1831. (b) Tchertchian, S.; Hartley, O.; Botti, P., *J. Org. Chem.* **2004**, *69*, 9208.
2. Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H., *J. Am. Chem. Soc.* **1992**, *114*, 10646.
3. Casi, G.; Hilvert, D., *Current Opinion in Structural Biology* 2003, Vol. 13, 589.
4. Kent, S., *J. Pept. Sci.* **2003**, *9*, 574.
5. Ma, Y.; Zhao, Y. F., *Chinese Sci. Bull.* **2003**, *48*, 1.
6. Tam, J. P.; Xu, J.; Eom, K. D., *Biopolymers* **2001**, *60*, 194.
7. Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. H., *Science* **1994**, *266*, 776.
8. Muir, T. W.; Sondhi, D.; Cole, P. A., *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 6705.

9. David, R.; Richter, M. P. O.; Sickinger, A. G., *Eur. J. Biochem.* **2004**, *271*, 663.
10. Guo, L.; Funakoshi, S.; Fujii, N.; Yajima, H., *Chem. Pharm. Bull.* **1988**, *36*, 4989.
11. Yajima, H.; Fujii, N.; Funakoshi, S.; Watanabe, T.; Murayama, E.; Otaka, A., *Tetrahedron* **1988**, *44*, 805.
12. Cardona, V. M. F.; Hartley, O.; Botti, P., *J. Pept. Res.* **2003**, *61*, 152.
13. Low, D. W.; Hill, M. G.; Carrasco, M. R.; Kent, S. B. H.; Botti, P., *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 6554.
14. Hruby, V. J., *Life Sciences* **1982**, *31*, 189.
15. Chorev, M.; Roubini, E.; McKee, R. L.; Gibbons, S. W.; Goldman, M. E.; Caulfield, M. P.; Rosenblatt, M., *Biochemistry* **1991**, *30*, 5968.
16. Botti, P.; Pallin, T. D.; Tam, J. P., *J. Am. Chem. Soc.* **1996**, *118*, 10018.
17. Zhang, L. S.; Tam, J. P., *J. Am. Chem. Soc.* **1997**, *119*, 2363.
18. Camarero, J. A.; Pavel, J.; Muir, T. W., *Angew. Chem., Int. Ed.* **1998**, *37*, 347.
19. Shao, Y.; Lu, W.; Kent, S. B. H., *Tetrahedron Lett.* **1998**, *39*, 3911.
20. Canne, L. E.; Bark, S. J.; Kent, S. B. H., *J. Am. Chem. Soc.* **1996**, *118*, 5891.
21. Wood, R. J.; Pascoe, D. D.; Brown, Z. K.; Medlicott, E. M.; Kriek, M.; Neylon, C.; Roach, P. L., *Bioconj. Chem.* **2004**, *15*, 366.
22. Lue, R. Y. P.; Chen, G. Y. J.; Hu, Y.; Zhu, Q.; Yao, S. Q., *J. Am. Chem. Soc.* **2004**, *126*, 1055.
23. McCaldon, P.; Argos, P., *Proteins-Struct. Funct. Genetics* **1988**, *4*, 99.
24. Offer, J.; Dawson, P. E., *Org. Lett.* **2000**, *2*, 23.
25. Vizzavona, J.; Dick, F.; Vorherr, T., *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1963.
26. Offer, J.; Boddy, C. N. C.; Dawson, P. E., *J. Am. Chem. Soc.* **2002**, *124*, 4642.
27. Kawakami, T.; Aimoto, S., *Tetrahedron Lett.* **2003**, *44*, 6059.
28. Clive, D. L. J.; Hisaindee, S.; Coltart, D. M., *J. Org. Chem.* **2003**, *68*, 9247.

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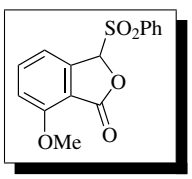
7-Methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone



[65131-09-1] $C_{15}H_{12}O_5S$ (MW 304.34)

InChI = 1/C15H12O5S/c1-19-12-9-5-8-11-13(12)14(16)20-15(11)21(17,18)10-6-3-2-4-7-10/h2-9,15H,1H3

InChIKey = BNOAFLKWYXXZHU-UHFFFAOYAL

(regioselective synthesis of 1,4-dihydroxy-2,3-disubstituted naphthalenes)

Physical Data: colorless solid; mp 176–177 °C.

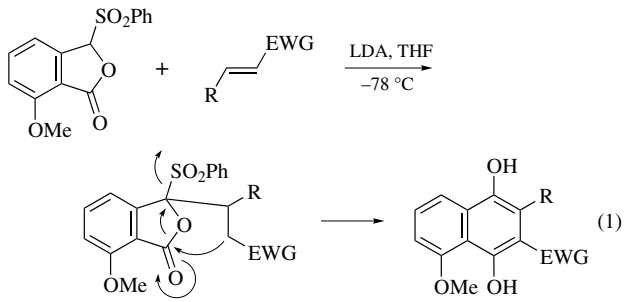
Solubility: partially sol THF; sol acetone.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.10 (s, 1H), 7.04 (d, J = 8 Hz, 1H), 7.40–7.92 (m, 7H).

Preparative Methods: ethyl 2-methoxy-6-methylbenzoate is oxidized via the dibromide to the corresponding 3-hydroxyisobenzofuranone, which is subsequently treated with thiophenol and catalytic acid. Oxidation to the sulfone is accomplished with either *m*-chloroperbenzoic acid or hydrogen peroxide.[1a] An alternative one-step method utilizing the requisite phthaldehydic acid has also been described.[2]

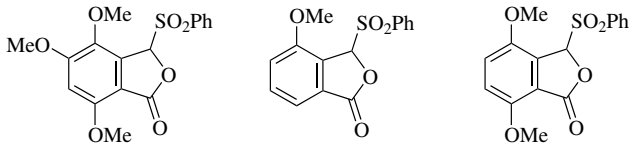
Handling, Storage, and Precaution: apparently stable at rt and requires no special handling or precautions.

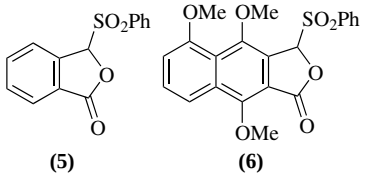
Aromatic Annulation. 7-Methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**1**) can be deprotonated at −78 °C with either lithium diisopropylamide or lithium *tert*-butoxide to form a soluble yellow anion which can be utilized as an effective nucleophile in the Michael reaction. The initial anionic adduct cyclizes with concomitant elimination of benzenesulfinic acid to yield a 1,4-dihydroxynaphthalene which is unambiguously disubstituted at the 2- and 3-positions (eq 1).[1b]



The 1,4-dihydroxynaphthalene products are susceptible to air oxidation and are frequently protected as the 1,4-dimethoxy derivatives. Alternatively, they may be intentionally oxidized to the naphthoquinones. A variety of acyclic and cyclic Michael acceptors participate in this reaction and yields are generally good. A few representative examples are seen in Table 1.[1b,3]

In fact, (**1**) represents a group of reagents (**2**)–(**6**) all having the 3-(phenylsulfonyl)isobenzofuranone moiety and all capable of the aromatic annulation reaction previously discussed.[1b,4–6]



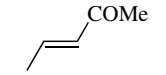
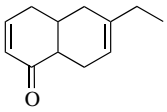
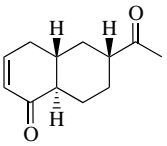
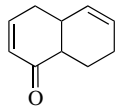
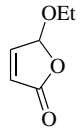
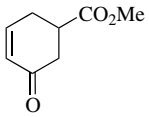


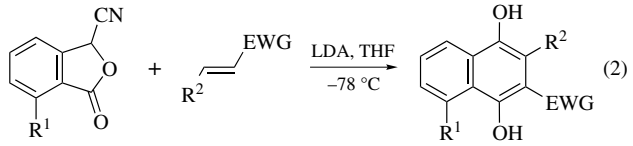
Under conditions similar to those described above, these compounds have been frequently utilized as building blocks for the synthesis of a wide range of molecules in the anthracyclinone family.

Alternative Reagents. 3-Cyanoisobenzofuranones have also been synthesized and shown to be useful in identical aromatic

annulation reactions (eq 2).[7] Moreover, in several direct comparisons of 3-cyano vs. 3-phenylsulfonyl, the cyano version generally provides higher yields of the desired product.[8] Nevertheless, on a large scale the liability of cyanide waste streams could be an important negative factor.

Table 1 Examples of michael acceptors which react with (**1**)

Michael acceptor	Yield (%)
	68
	91
	93
	84
	74
	85



(2)

Related Reagents. Similar aromatic annulations have been reported with a number of conceptually related reagents,[1b,9] the common thread of these methods being regioselective installation of substituents in the 2- and 3-positions of the newly formed naphthalene.

1. (a) Hauser, F. M.; Rhee, R. P., *J. Org. Chem.* **1980**, *45*, 3061. (b) Hauser, F. M.; Rhee, R. P., *J. Org. Chem.* **1978**, *43*, 178.
2. Kadiyala, V. S. N.; Murty, R. P.; Dutta, K.; Mal, D., *Synth. Commun.* **1990**, *20*, 1705.
3. (a) Hauser, F. M.; Prasanna, S., *Tetrahedron* **1984**, *40*, 4711. (b) Hauser, F. M.; Mal, D., *J. Am. Chem. Soc.* **1983**, *105*, 5688. (c) Hauser, F. M.; Prasanna, S.; Combs, D. W., *J. Org. Chem.* **1983**, *48*, 1328. (d) Hauser, F. M.; Prasanna, S., *J. Am. Chem. Soc.* **1981**, *103*, 6378. (e) Hauser, F. M.; Prasanna, S., *J. Org. Chem.* **1982**, *47*, 383.
4. Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M., *J. Org. Chem.* **1988**, *53*, 223.
5. Hauser, F. M.; Prasanna, S., *J. Am. Chem. Soc.* **1981**, *103*, 6378.
6. Hauser, F. M.; Caringal, Y., *J. Org. Chem.* **1990**, *55*, 555.
7. (a) Kraus, G. A.; Sugimoto, H., *Tetrahedron Lett.* **1978**, 2263. (b) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S., *J. Org. Chem.* **1983**, *48*, 3439.
8. (a) Li, T.-T.; Walsgrove, T., *Tetrahedron Lett.* **1981**, *22*, 3741. (b) Russell, R. A.; Pilley, B. A.; Irvine, R. W.; Warrener, R. N., *Aust. J. Chem.* **1987**, *40*, 311.
9. (a) Dodsworth, D. J.; Calcagno, M.-P.; Ehrmann, E. U.; Devadas, B.; Sammes, P. G., *J. Chem. Soc., Perkin Trans. 1* **1981**, 2120. (b) Dodd, J. H.; Weinreb, S. M., *Tetrahedron Lett.* **1979**, 3593. (c) Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H. F. M.; van Leusen, A. M., *Tetrahedron Lett.* **1978**, 2213.

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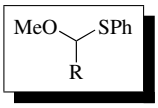
Methoxy(phenylthio)methane[1]

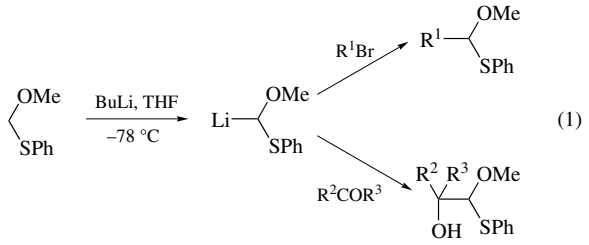


(R = H)
[13865-50-4] $C_8H_{10}OS$ (MW 154.25)
InChI = 1/C8H10OS/c1-9-7-10-8-5-3-2-4-6-8/h2-6H,7H2,1H3
InChIKey = QPXQVNXSQCRWEV-UHFFFAOYAO
(R = Li)
[95540-81-1] C_8H_9LiOS (MW 160.18)
InChI = 1/C8H9OS.Li/c1-9-7-10-8-5-3-2-4-6-8;/h2-7H,1H3;/
rC8H9LiOS/c1-10-8(9)11-7-5-3-2-4-6-7/h2-6,8H,1H3
InChIKey = LUOWYMGYDFUWGY-ICLVTCDLAP

(carbonyl anion equivalent useful for homologation and ring expansion)

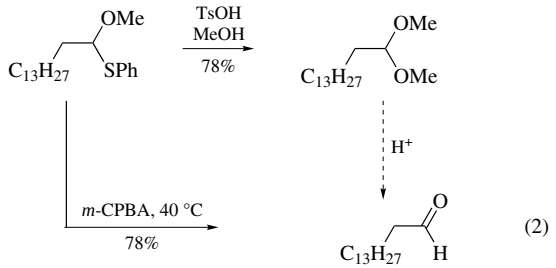
Physical Data: bp 113–114 °C/18 mmHg; *d* 1.047 g cm^{-3}.
Form Supplied in: neat liquid; commercially available.
Preparative Methods: via the base-catalyzed condensation of thiophenol and chloromethyl methyl ether[2] or via the boron trifluoride etherate-catalyzed condensation of thiophenol and dimethoxymethane.[3]
Handling, Storage, and Precautions: store under inert gas to avoid air oxidation of the sulfide. Hydrolysis of the reagent releases thiophenol (stench) which is known to be toxic. Use in a fume hood.

One-carbon Homologations. Methoxy(phenylthio)methane is a convenient one-carbon homologation reagent (also see 1,3-dithiane and methoxy(phenylthio)trimethylsilylmethane) with distinct differences from similar reagents derived from dithioacetals. Since the reagent possesses two different functional groups (methoxy and phenylthio), chemoselective manipulation of either functional group can be performed, resulting in an extremely versatile reagent. Methoxy(phenylthio)methane undergoes a facile deprotonation at the central carbon upon treatment with lithium diisopropylamide or butyllithium at −78 °C in THF. The resultant anion reacts with a variety of electrophiles such as alkyl halides, aldehydes, ketones, and epoxides (eq 1).[4] The thioacetal products thus formed can be chemically manipulated to afford a variety of homologated products.

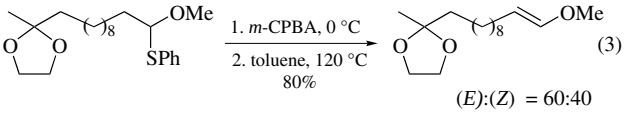


(1)

For example, treatment with *p*-toluenesulfonic acid in methanol affords dimethoxyacetals which can be further hydrolyzed to aldehydes (eq 2).[4] Aldehydes are also available in one step by oxidation of the sulfide to the sulfoxide with *m*-chloroperbenzoic acid and hydrolytic workup (eq 2).[4] Vinyl ethers are produced via a thermal elimination of benzenesulfenic acid (eq 3).[4] Alternately, the anion formed from the addition of methoxy(phenylthio)methyllithium to aldehydes can be treated with carbon disulfide and iodomethane to form a xanthate which when treated with tributylstannane effects a radical reductive elimination to form (*Z*)- and (*E*)-enol ethers (eq 4).[5]

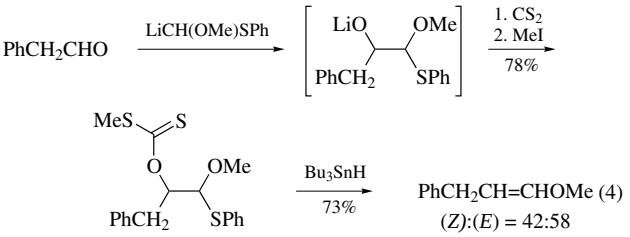


(2)

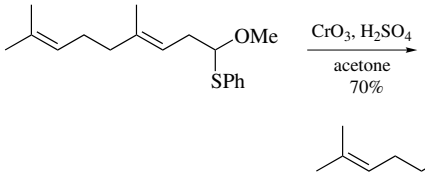


(3)

(*E*):(*Z*) = 60:40



In addition, carboxylic acids are accessible from the homologated thioacetals via Jones oxidation (eq 5).[4] Conjugate addition of methoxy(phenylthio)methyllithium to a vinyl sulfone, followed by Jones oxidation and elimination of benzenesulfenic acid, afforded a dienoic acid (eq 6).[6] A novel approach to α-phenylthioaldehydes, which involves a phenylthio migration, results from treating the adducts of methoxy(phenylthio)methyllithium and ketones with thionyl chloride in pyridine (eq 7)[7] or by treating the corresponding aldehyde adducts with methanesulfonyl chloride and triethylamine.[8] α-Phenylthioaldehydes thus obtained can be homologated further or converted to benzo[*b*]-thiophenes.[9]



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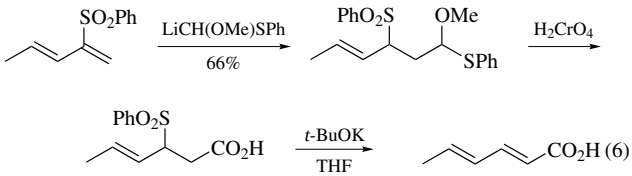
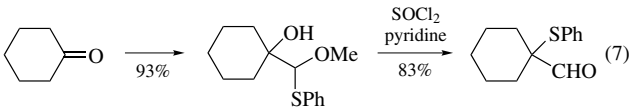


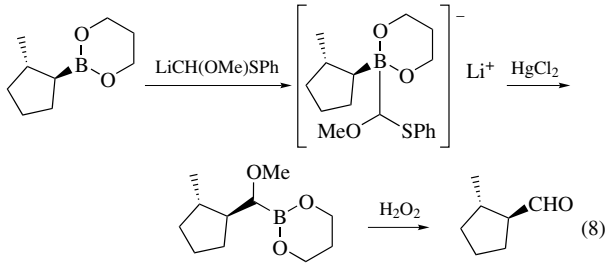
(6)

(2*E*,4*E*):(2*Z*,4*E*) = >98:<2



(7)

Alkylboronic esters available via the hydroboration of alkenes with dihaloboranes followed by alcoholysis can be homologated by reacting them with methoxy(phenylthio)methyllithium and treating the resulting ate complex with mercury(II) chloride followed by hydrogen peroxide (eq 8).[10] The use of an optically pure boronic ester affords optically pure aldehydes.[11]

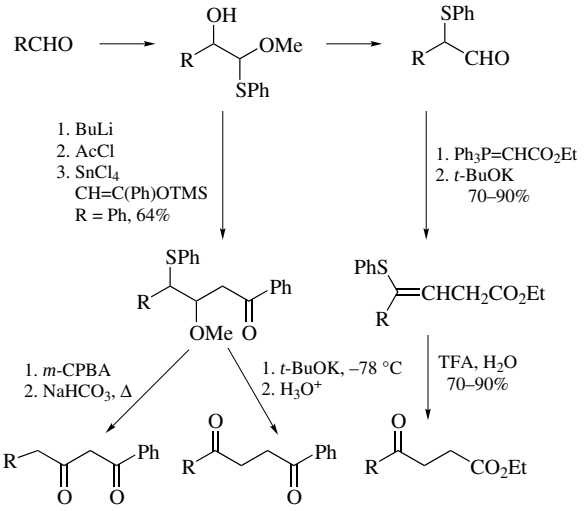


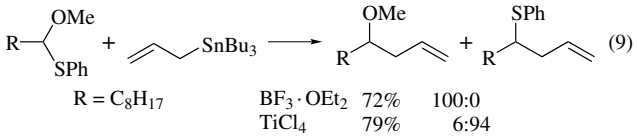
(8)

Homologation via Operations on Thioacetals. Four-carbon 1,3- and 1,4-dicarbonyl homologated compounds are accessible via subsequent manipulation of the adducts resulting from the condensation of methoxy(phenylthio)methyllithium with aldehydes. For example, reaction of the acylated adducts with enol silyl ethers under Lewis acid catalysis results in carbon–carbon bond formation and 1,2-migration of the phenylthio moiety. Such α-methoxy-γ-phenylthio ketones were converted into 1,3-dicarbonyl or 1,4-dicarbonyl compounds (Scheme 1).[12] Alternately, the α-phenylthioaldehydes can be converted into 1,4-dicarbonyl compounds (Scheme 1).

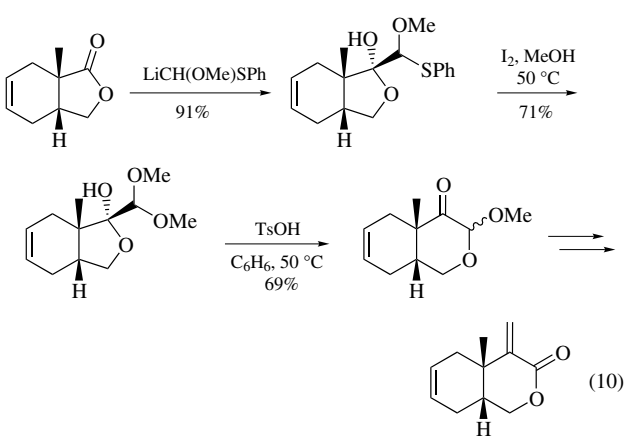
The use of the thioacetal products as electrophiles in Lewis acid-promoted reactions of allyl- and propargylstannanes allows access to three-carbon homologated methyl ethers or phenyl sulfides (eq 9). Employment of boron trifluoride etherate as the Lewis acid results in the selective cleavage of the phenylthio group to provide ether products. Similarly, the use of titanium(IV) chloride results in cleavage of the methoxy group and formation of

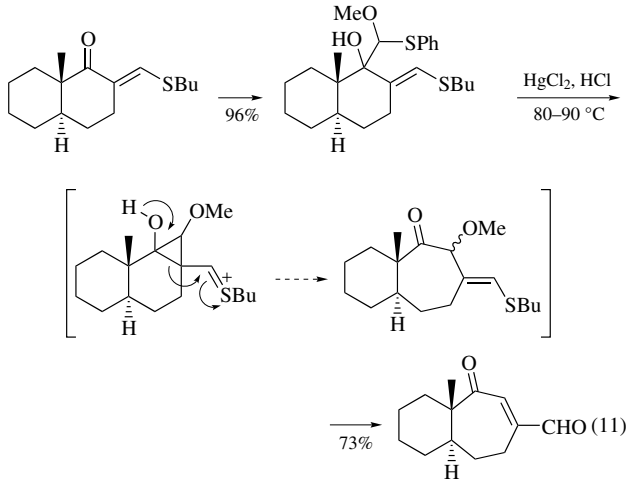
phenyl thiosulfide products. These reactions partially compensate for the inability of monoalkylated *O,S*-acetals to undergo dialkylation. Apparently, substitution of one of the alkylthio groups for methoxy sufficiently decreases the stability of an α-carbanion such that it cannot be formed, thus precluding its alkylation (in contrast, dithioacetals can be dialkylated).





Ring Expansions. Trost first demonstrated the advantages of methoxy(phenylthio)methane over bis(phenylthio)methane as an acyl anion equivalent in a synthesis of α-methylene-δ-lactones via the ring expansion of γ-butyrolactones (eq 10).[2a] Use of the *O,S*-acetal reagent avoided problems encountered with enolization. Methoxy(phenylthio)methane has also been utilized for the ring expansion of nonenolizable 2-*n*-butylthiomethylene cyclohexanones to 3-formyl-2-cyclohepten-1-ones (eq 11).[13]





1. Otera, J., *Synthesis* **1988**, 95.
2. (a) Trost, B. M.; Miller, C. H., *J. Am. Chem. Soc.* **1975**, *97*, 7182. (b) Oae, S.; Masuda, T.; Tsujihara, K.; Furakawa, N., *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3586.
3. Hackett, S.; Livinghouse, T., *J. Org. Chem.* **1986**, *51*, 879.
4. Mandai, T.; Hara, K.; Nakajima, T.; Kawada, M.; Otera, J., *Tetrahedron Lett.* **1983**, *24*, 4993.
5. Vatele, J.-M., *Tetrahedron Lett.* **1984**, *25*, 5997.
6. Plobeck, N. A.; Bäckvall, J.-E., *J. Org. Chem.* **1991**, *56*, 4508.
7. (a) de Groot, A.; Jansen, B. J. M., *Tetrahedron Lett.* **1981**, *22*, 887. (b) Jansen, B. J. M.; Peperzak, R. M.; de Groot, A., *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 489.
8. Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H., *J. Am. Chem. Soc.* **1988**, *110*, 5209.
9. de Groot, A.; Jansen, B. J. M., *Synthesis* **1985**, 434.
10. Brown, H. C.; Imai, T., *J. Am. Chem. Soc.* **1983**, *105*, 6285.
11. Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B., *J. Am. Chem. Soc.* **1985**, *107*, 4980.
12. Sato, T.; Inoue, M.; Kobara, S.; Otera, J.; Nozaki, H., *Tetrahedron Lett.* **1989**, *30*, 91.
13. (a) Guerrero, A.; Parrilla, A.; Camps, F., *Tetrahedron Lett.* **1990**, *31*, 1873. (b) Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, A.; Tatsuoka, T.; Meinwald, J., *J. Org. Chem.* **1986**, *51*, 773.

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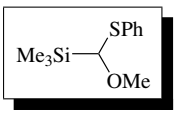
Methoxy(phenylthio)trimethylsilylmethane



[88738-21-0] $C_{11}H_{18}OSSi$ (MW 226.45)

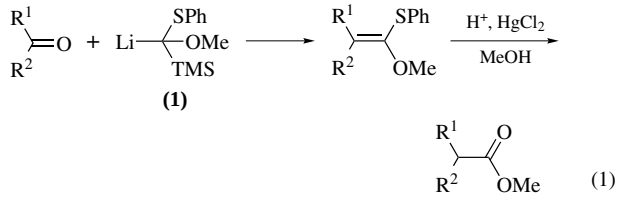
InChI = 1/C11H18OSSi/c1-12-11(14(2,3)4)13-10-8-6-5-7-9-10/h5-9,11H,1-4H3

InChIKey = SQOUWJXFDOXOAW-UHFFFAOYAA

(convenient homologation reagent for carbonyl compounds and alkyl halides; acyl anion equivalent)

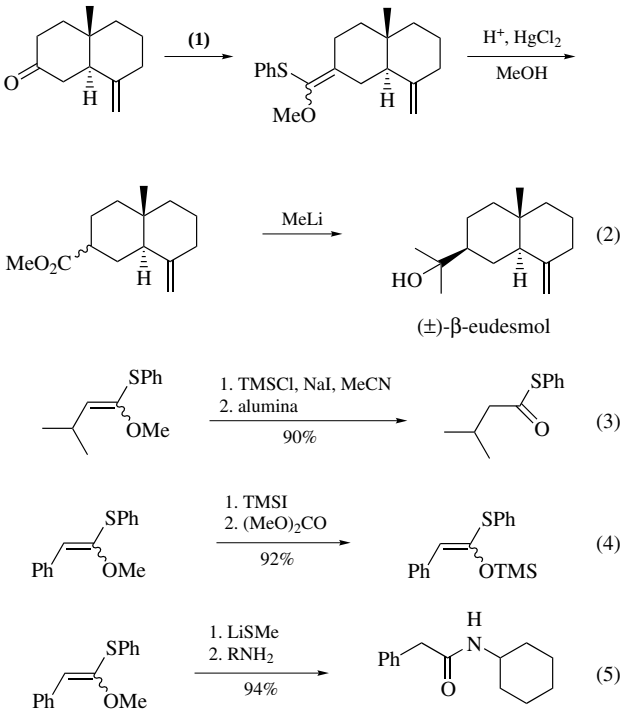
Physical Data: bp 120–122 °C/10 mmHg.
Solubility: sol ether, THF, dioxane, methanol, ethanol, benzene, hexane.
Form Supplied in: colorless liquid.
Preparative Method: from methoxy(phenylthio)methyllithium with chlorotrimethylsilane.[1]

Homologation of Carbonyl Compounds. Methoxy(phenylthio)trimethylsilylmethyllithium (**1**), an acyl anion equivalent, is generated by treating methoxy(phenylthio)trimethylsilylmethane with butyllithium at −80 °C in THF. This anion adds to carbonyl compounds in 1,2-fashion, providing ketene *O,S*-acetals via Peterson alkenation (eq 1).[1a] The ketene *O,S*-acetals thus obtained are converted to methyl esters by methanolysis in the presence of hydrogen chloride and mercury(II) chloride This procedure was applied to the synthesis of (±)-β-eudesmol (eq 2).[1a]



(1)

Cleavage of the ketene *O,S*-acetals under neutral or mildly basic conditions can be executed by using iodotrimethylsilane to give the phenyl thioester or the ketene *O*-silyl,*S*-acetal (eqs 3 and 4).[2] In addition, amides can be prepared by sequential treatment of ketene *O,S*-acetals with lithium thiomethoxide in HMPA followed by addition of an amine (eq 5).[2]



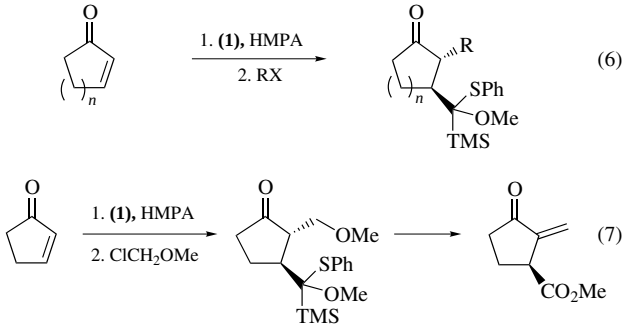
(2)

(3)

(4)

(5)

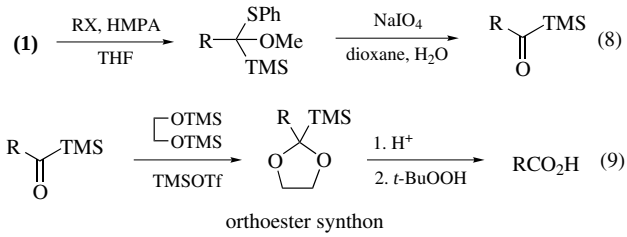
The reaction of anion (**1**) with cyclic α,β-unsaturated ketones provides 1,4-addition products in the presence of HMPA (eqs 6 and 7).[3] The resulting enolate can be trapped with various alkyl halides to give α- and β-disubstituted cyclic ketones with the *trans* configuration. This protocol was successfully applied to syntheses of sarkomycin and prostaglandin.[4]



(6)

(7)

Homologation of Alkyl Halides. Carbanion (**1**) serves as an acylsilane anion equivalent in reactions with alkyl halides. The alkylation proceeds smoothly at −40 °C in the presence of HMPA to provide *O,S*-acetals which are easily transformed into acylsilanes via oxidation with sodium periodate in wet dioxane (eq 8).[5] Acetalization of acylsilanes gives α-trimethylsilyl acetals, which are orthoester synthetic equivalents (eq 9).[6] The synthesis of isocarbacyclin was achieved by using this procedure.

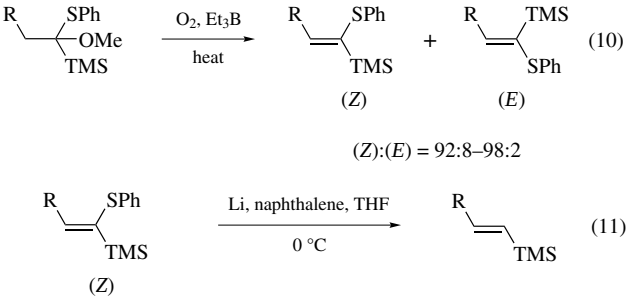


(8)

(9)

orthoester synthon

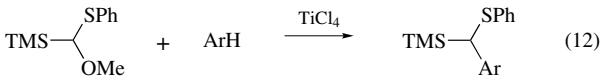
In another synthetic application, the alkylation products of (**1**) undergo facile thermal elimination of methanol to afford (*Z*)-1-phenylthio-1-trimethylsilylalkenes in good yields with high stereoselectivity (eq 10).[7] The elimination is facilitated by oxygen and is further accelerated by the addition of triethylborane, which implies the involvement of a radical pathway. The resulting (*Z*)-1-phenylthio-1-trimethylsilylalkenes are transformed into (*E*)-vinylsilanes by reductive cleavage of the thiophenyl group with lithium naphthalenide (eq 11).[7]



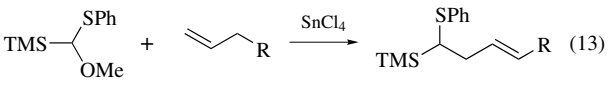
(10)

(11)

Homologation of Arenes and Alk-1-enes. Methoxy(phenylthio)trimethylsilylmethane undergoes Friedel–Crafts reaction with arenes in the presence of Lewis acids such as titanium(IV) chloride and tin(IV) chloride to afford (aryl(phenylthio)methyl)-trimethylsilanes (eq 12).[8] This reagent also reacts with terminal alkenes in the presence of $SnCl_4$ to give ene products (eq 13).[8]



(12)



(13)

1. (a) Groot, A. D.; Jansen, B. J. M., *Synth. Commun.* **1983**, *13*, 985. (b) Rawal, V. H.; Akiba, M.; Cava, M. P., *Synth. Commun.* **1984**, *14*, 1129.
2. Hackett, S.; Livinghouse, T., *Tetrahedron Lett.* **1984**, *25*, 3539.
3. (a) Otera, J.; Niibo, Y.; Aikawa, H., *Tetrahedron Lett.* **1987**, *28*, 2147. (b) Otera, J.; Niibo, Y.; Nozaki, H., *J. Org. Chem.* **1989**, *54*, 5003.
4. Otera, J.; Niibo, Y.; Nozaki, H., *Tetrahedron Lett.* **1992**, *33*, 3655.
5. Mandai, T.; Yamaguchi, M.; Nakayama, Y.; Otera, J.; Kawada, M., *Tetrahedron Lett.* **1985**, *26*, 2675.
6. Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J.; Saito, S.; Moriwake, T., *J. Org. Chem.* **1990**, *55*, 5671.
7. Mandai, T.; Kohama, M.; Sato, H.; Kawada, M.; Tsuji, J., *Tetrahedron* **1990**, *46*, 4553.
8. Han, D. I.; Oh, D. Y., *Synth. Commun.* **1989**, *19*, 2213.

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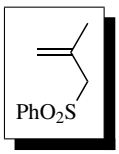
2-Methylallyl Phenyl Sulfone



[49639-05-6] $C_{10}H_{12}O_2S$ (MW 196.27)

InChI = 1/C10H12O2S/c1-9(2)8-13(11,12)10-6-4-3-5-7-10/h3-7H,1,8H2,2H3

InChIKey = OFHZALKLLSXZST-UHFFFAOYAG

(reagent used as an isobutene component via its 1,1- or 1,3-dipole synthon in a variety of reactions)

Alternate Names: methallyl phenyl sulfone; 1-(phenylsulfonyl)-2-methyl-2-propene)

Physical Data: mp 44–44.5 °C.

Solubility: soluble in methylene chloride, chloroform, THF, methanol, and other common organic solvents.

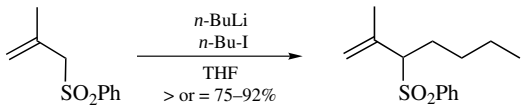
Form Supplied in: white solid or needle crystal (after recrystallization).

Preparative Methods: Different methods are reported for reagent preparation: sulfonylation of methallyl chloride,[1] oxidation of the corresponding sulfide,[2] sequential bromination-sulfonylation of methallyl alcohol,[3] and palladium-catalyzed sulfonylation of the corresponding α-nitro olefin.[4] Sulfonylation of methallyl chloride with sodium benzenesulfinate is the recommended preparation for this reagent.[1b]

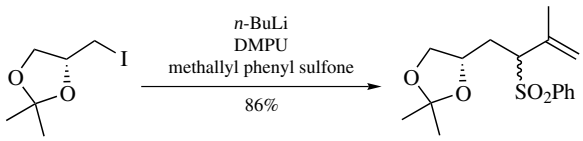
Purification: recrystallization from isopropanol.

Handling, Storage, and Precautions: Pressure may develop in a container stored at room temperature for extended time; therefore precaution should be taken before opening. The pure reagent is stable at room temperature and not sensitive to air, but cold storage under an inert atmosphere is deemed prudent.

Alkylation. Allylic sulfones have proven particularly useful in organic synthesis by exploiting their character as 1,1- or 1,3-dipole synthon.[5,6] For example, methallyl phenyl sulfone is typically alkylated with alkyl halides. The sulfone group is ultimately easily removed by reduction, elimination, or substitution. Alkylation with iodobutane[5,7] using *n*-butyllithium gave the α-butylated allylic sulfone product (eq 1), and the phenyl sulfone group was subsequently removed via palladium-catalyzed nuleophilic substitution to give 75–92% overall yield.[5a] The total synthesis of epothilones B and D featured alkylation of methallyl phenyl sulfone with the iodoacetonide in 86% yield (eq 2), followed by desulfonylation using tributyltin hydride.[7b] Interestingly, the allylic sufone was used as a carbon nucleophile for Mitsunobu-type alkylation (eq 3).[8]



(1)



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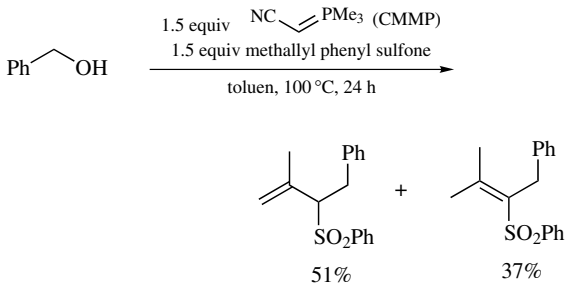
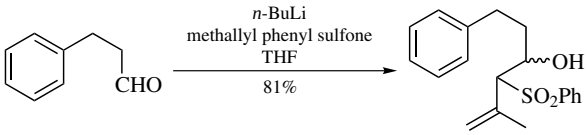


(3)

1,2-Addition. 1,2-Addition of an α-sulfonyl carbanion to aldehydes or epoxides is a common strategy for carbon-carbon bond formation. The addition to 3-phenyl propionaldehyde provided the homoallylic alcohol (eq 4) in high yield.[5b] Diastereoselective addition to epoxides exploited use of the sulfonyl dianion, which reacted with cyclohexene epoxide to provide the *syn*-dominated product in 58% yield (eq 5). Acyclic epoxides performed even better (eq 6).[9]



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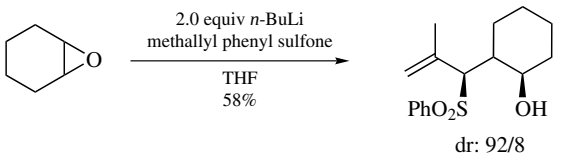

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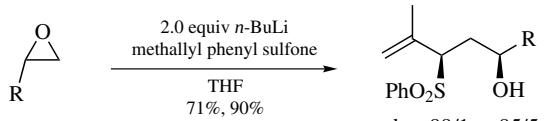
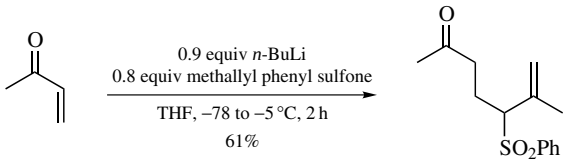


(6)

R = Ph or $CH_2CH_2CH{=}CH_2$

Michael Addition. Methallyl phenyl sulfone has been a good partner with a variety of different Michael receptors. Addition to enones using *n*-BuLi as base at −78 °C gave the desired products in good yields.[1b,10] Methyl vinyl ketone afforded the Michael adduct in 61% yield (eq 7).[1b] Reaction of methallyl sulfone with 2-hexenone and 2-methyl-2-pentenone in the presence of HMPA provided the conjugate addition products in 91% yield and 79% yield, respectively (eqs 8 and 9).[10,11a]



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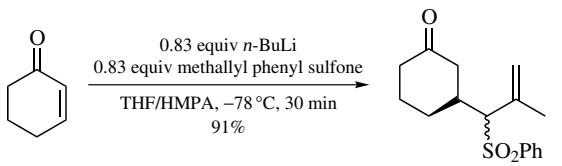

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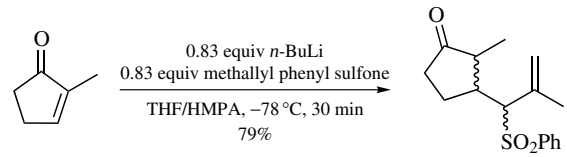
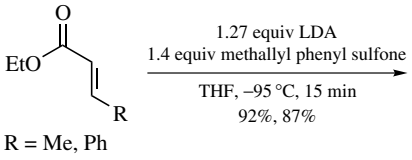
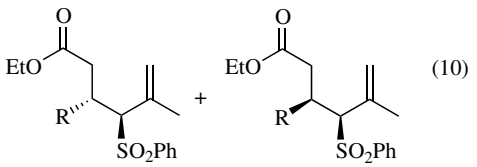


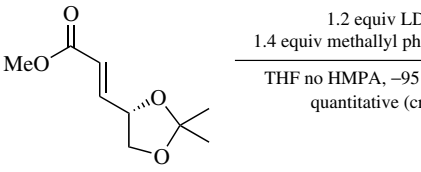
(9)

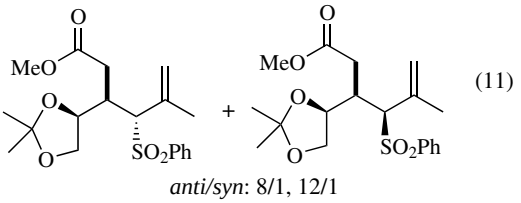
Michael addition to substituted enoates has proven diastereoselective.[11] Ethyl (*E*)-crotonate or ethyl (*E*)-cinnamate afforded conjugate addition adducts in 92% yield and 87% yield with *anti*/*syn*-diastereomeric ratios of 85/15 and 100/0, respectively (eq 10); whereas in the presence of HMPA the diastereoselectivity was reversed.[11a] With the γ-oxygenated enoate, *anti*-diastereoselectivity resulted; HMPA improved the selectivity from 8/1 to 12/1 (eq 11).[11b] Similar results were obtained with a conjugated lactone (eq 12).[11a] Ethyl ynoate also acted as a reactive Michael receptor for the methallyl sulfone (eq 13).[12] Other conjugated substrates such as nitroolefins[13a,b] and acrylonitrile[13c] proved to be appropriate Michael receptors as well.



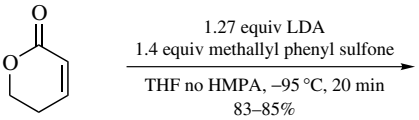


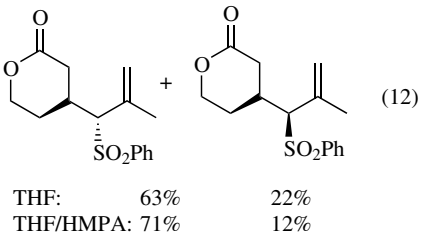
(10)



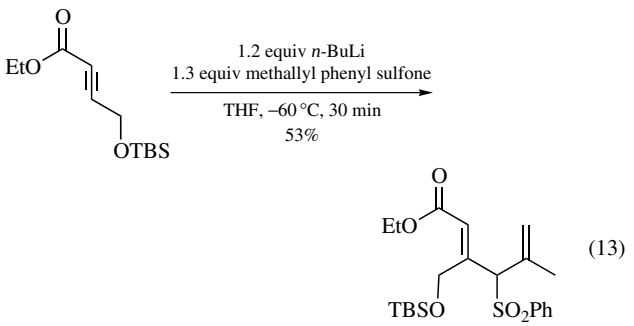


(11)





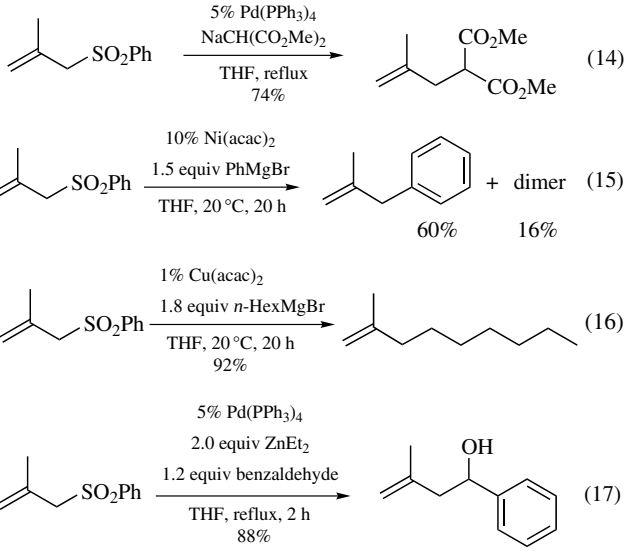
(12)



(13)

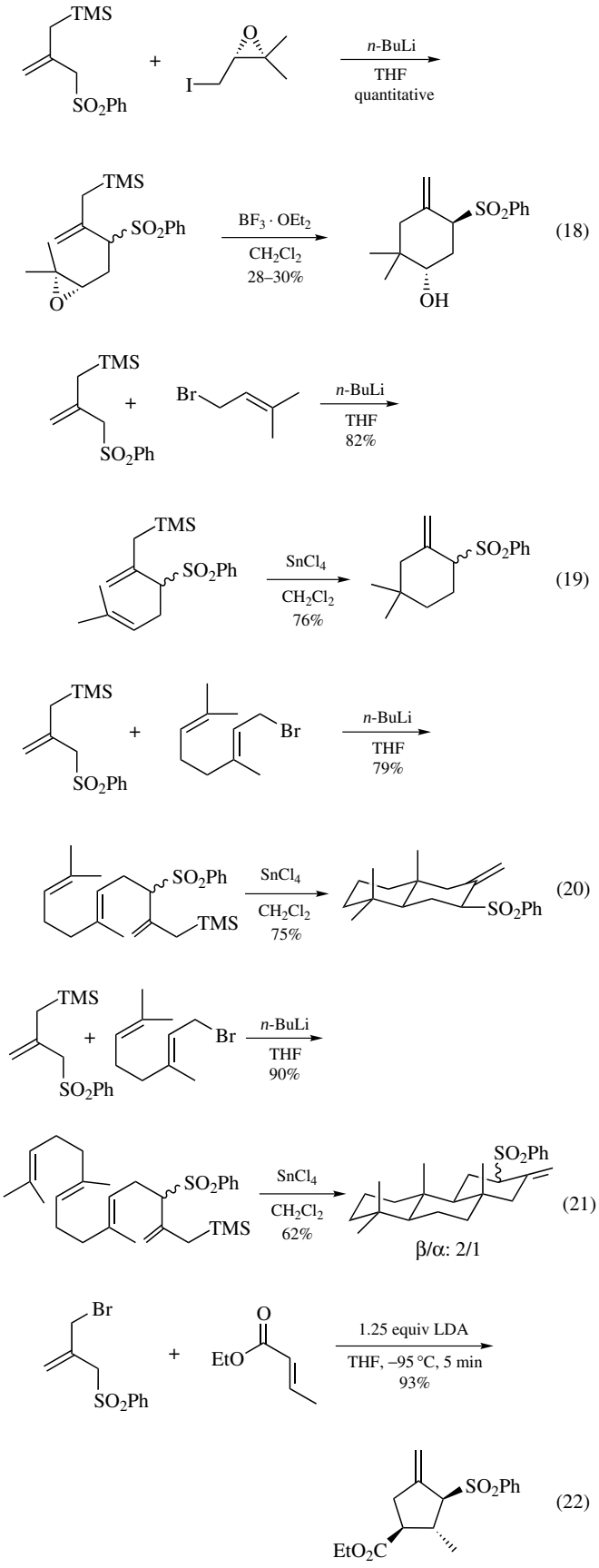
Transition Metal-catalyzed Reactions. Methallyl phenyl sulfone has been a useful allylation reagent for transition metal-catalyzed reactions. Palladium-catalyzed Tsuji-Trost reaction

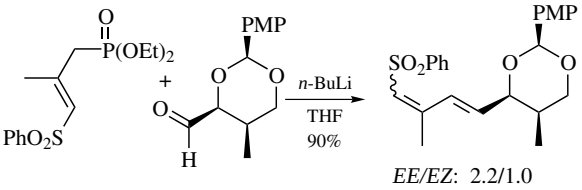
with the soft nucleophile sodium dimethyl malonate gave the allylated malonate in 74% yield (eq 14).[5a] Similar reactions were effected by a nickel catalyst.[14] Metal-catalyzed coupling reactions with Grignard reagents are also useful allylations. Nickel catalysis with phenylmagnesium bromide gave the methallyl benzene in 60% yield along with the dimerized sulfone as an impurity (eq 15), whereas an iron catalyst was more effective.[15] Copper-catalyzed coupling with hexyl Grignard reagent gave the desired allylic product in 92% yield (eq 16).[1a] The electrophilic character of π-allyl transition metal reactions was inverted by using diethylzinc to provide the nucleophilic allyl anion equivalent, which reacted with benzaldehyde to deliver the homoallylic alcohol in 88% yield (eq 17).[16a] Samarium diiodide gave the Barbier-type reaction with *n*-hexanal in 88% yield.[16b] Tris(trimethylsilyl)silane also mediated the allylation reaction.[17]



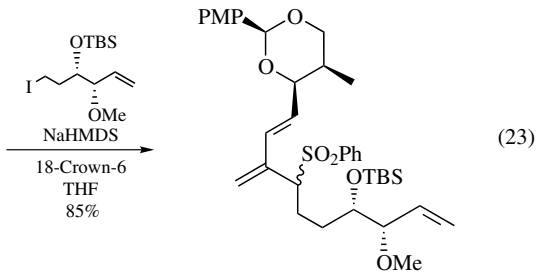
Bis-functional Reagents. Reagents bearing bis-functionalities often serve as useful conjunctive synthons in organic synthesis. Conjunctive reagents analogous to methallyl phenyl sulfone have been reported. TMS methallyl sulfone was directly prepared from conjugate addition of trimethylsilylmethyl cuprate to phenyl sulfonyl allene,[18b] as well as being obtainable from methallyl alcohol[18a] or methallyl chloride.[18c] The reagent was used to provide the enantiopure methylenecyclohexanol (eq 18)[18a] and the methylenecyclohexane (eq 19)[19] by α-sulfonyl alkylation with the iodoepoxide or the allylic bromide, respectively, followed by Lewis acid-induced cyclizations. The same sequence was applied to stereoselective synthesis of methylenedecahydronaphthalene (eq 20) as well as the methylenetetradecahydrophenanthrene (eq 21). This study indicated that the phenyl sulfone played an important role in the cyclization process.[19]

Bromo methallyl sulfone, prepared from methallyl phenyl sulfone,[6,20] has proven to be a good substrate for stereoselective synthesis of trisubstituted methylenecyclopentanes with a variety of different Michael receptors.[11,13] For example, the *trans trans*-trisubstituted methylenecyclopentane was efficiently prepared in 93% yield by a cascade Michael addition/cyclization beginning with ethyl (*E*)-crotonate (eq 22).[11a] The phosphonate sulfone reagent, readily available from methallyl phenyl sulfone, was used for the selective synthesis of 1,3-dienes.[6] The synthesis included two conjugative operations with dioxane aldehyde and the iodide (eq 23).





EE/EZ: 2.2/1.0



(23)

Related Reagents. Methallyl chloride; Methallyl Bromide; Methallyl Alcohol; 3-Chloro-2-chloromethyl-1-propene; 2-Methylene-1,3-propanediol.

1. (a) Julia, M.; Righini-Tapie, A.; Verpeaux, J.-N., *Tetrahedron* **1983**, *39*, 3283–3287. (b) Trost, B. M.; Schmuff, N. R., *J. Am. Chem. Soc.* **1985**, *107*, 396.
2. (a) Baechler, R. D.; Bentley, P.; Deuring, L.; Fisk, S., *Tetrahedron Lett.* **1982**, *23*, 2269. (b) Barton, D. H. R.; Li, W.; Smith, J. A., *Tetrahedron Lett.* **1998**, *39*, 7055.
3. Murakami, T.; Furusawa, K., *Synthesis* **2002**, 479.
4. Tamura, R.; Kai, Y.; Kakihana, M.; Hayashi, K.; Tsuji, M., *J. Org. Chem.* **1986**, *51*, 4375.
5. (a) Trost, B. M.; Schmuff, N. R.; Miller, M. J., *J. Am. Chem. Soc.* **1980**, *102*, 5979. (b) Trost, B. M.; Ghadiri, M. R., *J. Am. Chem. Soc.* **1986**, *108*, 1098.
6. Li, X.; Lantrip, D.; Fuchs, P. L., *J. Am. Chem. Soc.* **2003**, *125*, 14262.
7. (a) Jończyk, A.; Radwan-Pytlewski, T., *J. Org. Chem.* **1983**, *48*, 910. (b) Martin, N.; Thomas, E. J., *Tetrahedron Lett.* **2001**, *42*, 8373.
8. Uemoto, K.; Kawahito, A.; Matsushita, N.; Sakamoto, I.; Kaku, H.; Tsunoda, T., *Tetrahedron Lett.* **2001**, *42*, 905.
9. Trost, B. M.; Merlic, C. A., *J. Am. Chem. Soc.* **1988**, *110*, 5216.
10. Hirama, M., *Tetrahedron Lett.* **1981**, *22*, 1905.
11. (a) Ghera, E.; Yechezkel, T.; Hassner, A., *J. Org. Chem.* **1996**, *61*, 4959. (b) Yechezkel, T.; Ghera, E.; Ramesh, N. G.; Hassner, A., *Tetrahedron: Asymmetry* **1996**, *7*, 2423.
12. Nakache, P.; Ghera, E.; Hassner, A., *Tetrahedron Lett.* **2000**, *41*, 5583.
13. (a) Ghera, E.; Ben-Yaakov, E.; Yechezkel, T.; Hassner, A., *Tetrahedron Lett.* **1992**, *33*, 2741. (b) Ghera, E.; Yechezkel, T.; Hassner, A., *J. Org. Chem.* **1993**, *58*, 6716. (c) Jończyk, A.; Radwan-Pytlewski, T., *Polish J. Chem.* **1995**, *69*, 1161.
14. (a) Cuvigny, T.; Julia, M., *J. Organomet. Chem.* **1983**, *250*, C21–C24. (b) Cuvigny, T.; Julia, M., *J. Organomet. Chem.* **1986**, *317*, 383.
15. Gai, Y.; Julia, M.; Verpeaux, J.-N., *Bull. Soc. Chem. Fr.* **1996**, *133*, 805.
16. (a) Clayden, J.; Julia, M., *J. Chem. Soc., Chem. Commun.* **1994**, 1905. (b) Clayden, J.; Julia, M., *J. Chem. Soc., Chem. Commun.* **1994**, 2261.
17. Chatgilialoglu, C.; Alberti, A.; Ballestri, M.; Macciantelli, D., *Tetrahedron Lett.* **1996**, *37*, 6391.
18. (a) Xiao, X.-Y.; Park, S.-K.; Prestwich, G. D., *J. Org. Chem.* **1988**, *53*, 4869. (b) Harmata, M.; Herron, B. F., *Synthesis* **1993**, 202. (c) Kang, K.-T.; U, J. S.; Park, D. K.; Kim, J. G.; Kim, W. J., *Bull. Korean Chem. Soc.* **1995**, *16*, 464.
19. Kang, K.-T.; Park, D. K.; Lee, S. J.; Sung, T. M., *Bull. Korean Chem. Soc.* **1996**, *17*, 777.
20. (a) Tabush, I.; Tamaru, Y.; Yoshida, Z., *Tetrahedron*, **1974**, *30*, 1457. (b) Breulles, P.; Uguen, D., *Tetrahedron Lett.* **1987**, *28*, 6053.

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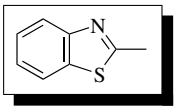
2-Methylbenzothiazole[1]

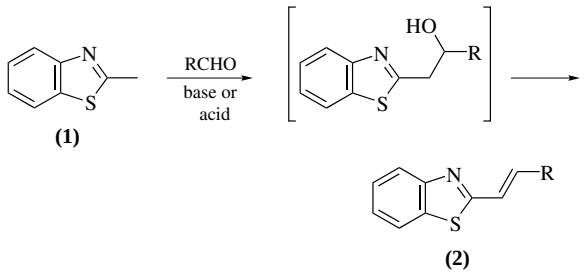


[120-75-2] C_8H_7NS (MW 149.23)
InChI = 1/C8H7NS/c1-6-9-7-4-2-3-5-8(7)10-6/h2-5H,1H3
InChIKey = DXYYSGDWQCSKKO-UHFFFAOYAE

(the α-lithio derivative represents a masked enolate;[2] the α-trimethylsilyl derivative is used for Peterson alkenations[3])

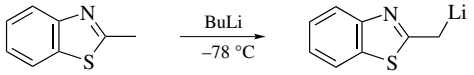
Physical Data: mp 14 °C; bp 238 °C/765 mmHg; bp 151 °C/15 mmHg; *d* 1.1763 g cm^{-3}; n_D 1.6092.
Solubility: insol H_2O; sol ethanol; very sol diethyl ether, THF.
Form Supplied in: liquid; widely available.
Analysis of Reagent Purity: ^{1}H and ^{13}C NMR spectra.
Purification: distillation under reduced pressure.
Handling, Storage, and Precautions: should be freshly distilled before use for best results. Toxic by inhalation, in contact with skin, and if swallowed. Use in a fume hood.

Introduction. 2-Methylbenzothiazole (**1**) has been used[4] in base- and acid-mediated condensations with aldehydes to give products which normally undergo dehydration in situ to give alkenes (**2**) (eq 1).



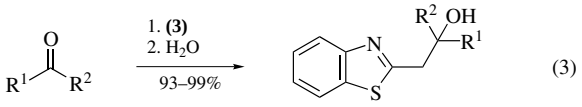
(1) **(2)** (1)

α-Lithio-2-methylbenzothiazole.[1] This reagent is readilys available by lithiation of 2-methylbenzothiazole (**1**) with butyllithium at −78 °C (eq 2),[1,3] which gives rise to a yellow precipitate (indicating the formation of the organometallic compound) when diethyl ether is used as a solvent or to a clear light-brown solution in THF or 1,2-dimethoxyethane.



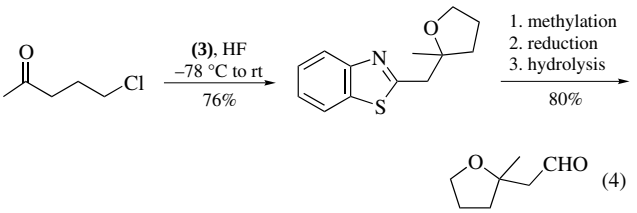
(1) **(3)** (2)

α-Lithio-2-methylbenzothiazole (**3**) reacts with various electrophiles such as aldehydes and ketones[2] to afford 2-(2-hydroxyalkyl)benzothiazoles in high yields (eq 3).



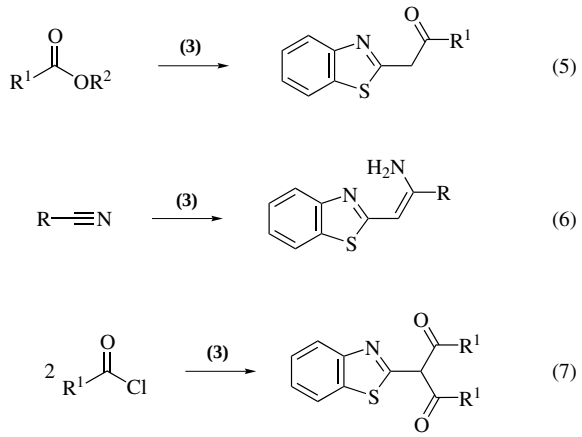
(3)

Chikashita et al.[2] have demonstrated the synthetic equivalence of (**3**) to a masked enolate anion through the liberation of the aldehyde by cleavage of the benzothiazole ring (eq 4).



(4)

More recently, Lochon et al.[5] have reported the reaction of (**3**) with other electrophiles such as esters (eq 5) and nitriles (eq 6). When the same reaction is carried out with acyl chlorides, bisacylated compounds are obtained (eq 7).

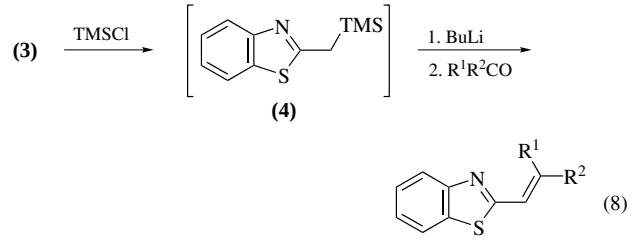


(5)

(6)

(7)

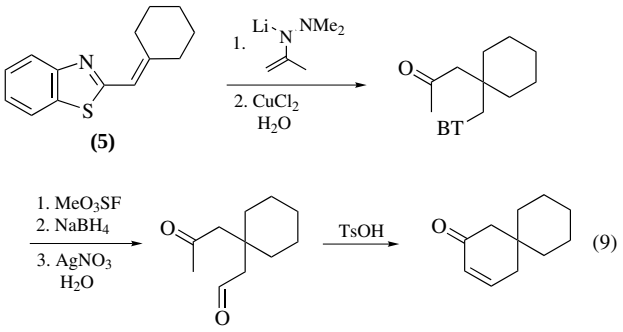
2-(Trimethylsilylmethyl)benzothiazole. α-Lithio-2-methylbenzothiazole (**3**) is quantitatively silylated with chlorotrimethylsilane to give reagent (**4**), which can be further metalated and condensed with carbonyl compounds to give the corresponding alkenes (eq 8).[3] This two-carbon homologation sequence corresponds to a Peterson alkenation, i.e. it is an alternative to the Wittig and Horner–Emmons reactions.[6] Endocyclic analogs such as 2-(1-cyclohexenyl)- and 2-(1-cyclopentenyl)benzothiazoles are accessible via addition of 2-lithiobenzothiazole to corresponding cyclic ketones and subsequent dehydration.[3]



(4)

(8)

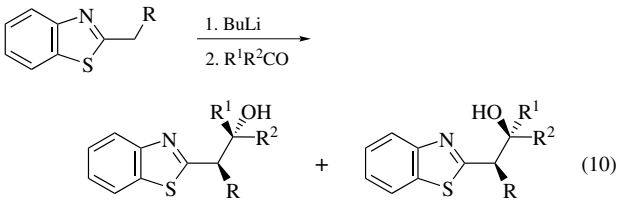
The vinylbenzothiazole (**5**), derived from cyclohexanone through (**4**), undergoes efficient conjugate addition reactions with a variety of alkyllithium reagents (alkyl, vinyl, phenyl, and allyl) as well as with acetone and acetaldehyde *N,N*-dimethylhydrazone anions.[7a] The resulting adduct carbanions may be protonated (MeOH) or alkylated in situ with methyl, allyl, and propargyl halides. The double bond of (**5**) can be hydrogenated (H_2, Pd/C, EtOH) smoothly without catalyst poisoning. Conversion of the benzothiazole moiety to the formyl group is accomplished by *N*-methylation ($MeOSO_2F$, CH_2Cl_2), reduction ($NaBH_4$, EtOH), and hydrolysis ($AgNO_3$, aq. MeCN, pH 7). Aldol cyclization of the liberated aldehyde onto the α- or β-acetonyl substituents provide effective methods for fused and spiro annulation of cyclohexenone or cyclopentenone rings (e.g. eq 9).[7b]



(5)

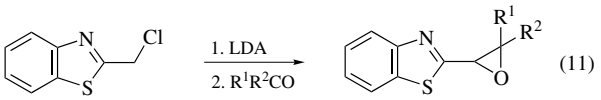
(9)

Other 2-Alkylbenzothiazoles. Florio et al.[8] have reported the metalation of 2-alkylbenzothiazoles (2-ethyl, 2-propyl, and 2-phenyl) to give the corresponding α-lithioalkylbenzothiazoles which undergo aldol condensations with carbonyl compounds (eq 10).



(10)

More recently,[9] the Darzens reaction between the lithio derivative of 2-chloromethylbenzothiazole (**6**) and carbonyl compounds to furnish epoxides has been described (eq 11).



(6)

(11)

Related Reagents. Benzothiazole; 2-Methyl-2-thiazoline; 5,6-Dihydro-2,4,4,6-tetramethyl-1,3(4*H*)-oxazine; 2,4,4-Trimethyl-2-oxazoline; 2-(Trimethylsilyl)thiazole.

1. For an extensive study on the metalation of 2-methylbenzothiazole with several reagents, see: Costa, M. V.; Lochon, P., *J. Organomet. Chem.* **1985**, *293*, 265.
2. Chikashita, H.; Ikegami, S.; Okumura, T.; Itoh, K., *Synthesis* **1986**, 375.
3. Corey, E. J.; Boger, D. L., *Tetrahedron Lett.* **1978**, 5.
4. Dryanska, V.; Ivanov, C., *Synthesis* **1976**, 37.
5. Costa, M. V.; Brembilla, A.; Roizard, D.; Lochon, P., *J. Heterocycl. Chem.* **1991**, *28*, 1541.

6. Knott, E. B., *J. Chem. Soc.* **1965**, 3793.
7. (a) Corey, E. J.; Boger, D. L., *Tetrahedron Lett.* **1978**, 9. (b) Corey, E. J.; Boger, D. L., *Tetrahedron Lett.* **1978**, 13.
8. (a) Epifani, E.; Florio, S.; Ingrosso, G., *Tetrahedron Lett.* **1987**, *28*, 6385. (b) Epifani, E.; Florio, S.; Ingrosso, G., *Tetrahedron* **1987**, *43*, 1937.
9. Florio, S.; Troisi, L., *Tetrahedron Lett.* **1992**, *33*, 7953.

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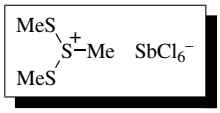
Methylbis(methylthio)sulfonium Hexachloroantimonate[1]



[56648-69-2] $C_3H_9Cl_6S_3Sb$ (MW 475.78)

InChI = 1/C3H9S3.6ClH.Sb/c1-4-6(3)5-2;;;;;;;/h1-3H3;6*1H;/q+1;;;;;;;+5/p-6/fC3H9S3.6Cl.Sb/h;6*1h;/qm;6*-1;m/rC3H9S3.Cl6Sb/c1-4-6(3)5-2;1-7(2,3,4,5)6/h1-3H3;/q+1;-1

InChIKey = ULSDXJWYPVAWDZ-GZUPUODLCT

(methylthiolating agent for several functional groups;[1] can induce cyclization of functionalized alkenes and alkynes[1])

Physical Data: mp 123–125 °C (dec).

Solubility: sol CH_2Cl_2, SO_2; reacts with H_2O, protic solvents, acetone, and other enolizable carbonyl derivatives.

Analysis of Reagent Purity: ^{1}H NMR spectrum at −50 °C in CD_2Cl_2 of the pure compound shows two signals at δ 3.6 and 3.0 with an intensity ratio 1:2.[2] At higher temperature in this solvent, as well as in other solvents (SO_2,[3] CD_3CN[4]), a single coalescence line is observed. This behavior is due to trace amounts of dimethyl disulfide impurities.[3]

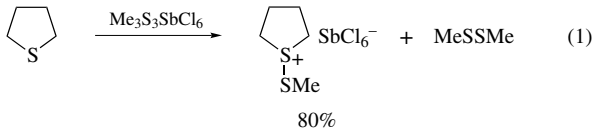
Preparative Methods: to an ice cooled solution of antimony(V) chloride (7.85 mmol) in anhydrous CH_2Cl_2 (5 mL), a solution of methanesulfenyl chloride (7.85 mmol) and dimethyl disulfide (7.85 mmol) in CH_2Cl_2 (10 mL) is added dropwise. The product partially precipitates from the solution. Addition of *n*-pentane causes complete precipitation of the hexachloroantimonate salt. The product (95% yield) is isolated by filtration in a dry box and can be used without any further purification.[3] Alternatively, to a well-stirred solution of dimethyl disulfide (0.1 mol) in dry CH_2Cl_2 (50 mL) is dropped at 0 °C a solution of $SbCl_5$ (0.1 mol) in dry CH_2Cl_2 (50 mL). After completion of the addition the salt starts crystallizing as yellowish needles. Addition of dry Et_2O completes the precipitation of the product (92% yield).[4]

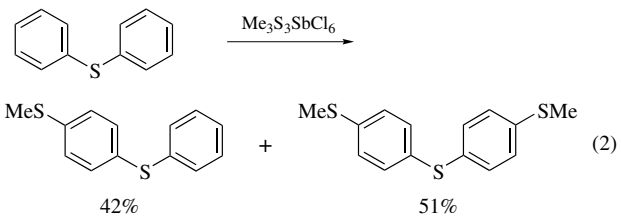
Purification: crystallization by solution in dry CH_2Cl_2 and addition of dry *n*-pentane or Et_2O.

Handling, Storage, and Precautions: stable for some months if stored in the refrigerator; sensitive to moisture, protic solvents, and enolizable carbonyl compounds.

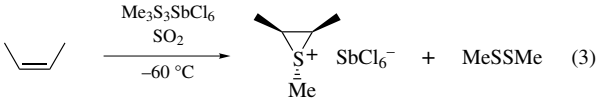
Functional Group Methylthiolation. The main feature of methylbis(methylthio)sulfonium hexachloroantimonate ($Me_3S_3SbCl_6$) is the easy transfer of a methylsulfenylium ion to a variety of functional groups more nucleophilic than the sulfur of dimethyl disulfide. The low nucleophilicity of the disulfide and of the hexachloroantimonate ion allows the isolation, or the characterization, of positively charged reaction products.

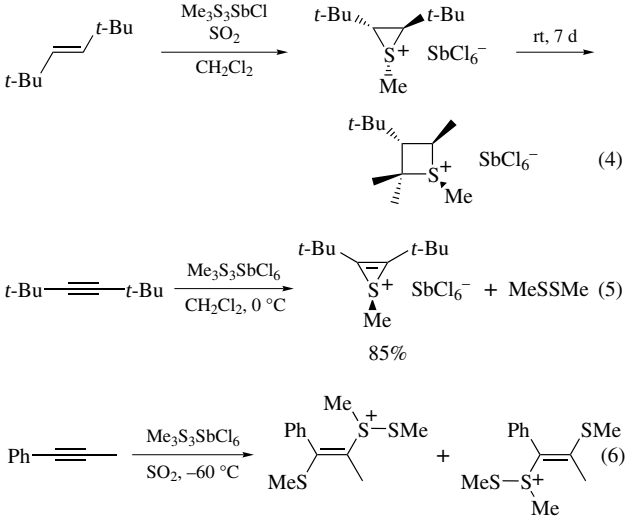
The methylthiolation of dialkyl or cyclic sulfides with $Me_3S_3SbCl_6$ proceeds smoothly at 0 °C in CH_2Cl_2 and gives methylthiosulfonium salts in good yields (60–80%).[5] Methylthiosulfonium salts can also be prepared by methylation of disulfides with trimethyloxonium salts.[6] However, the latter method cannot be applied to the synthesis of methylthiosulfonium salts derived from cyclic sulfides (eq 1). The reaction of $Me_3S_3SbCl_6$ with diphenyl sulfide gives an almost equimolar mixture of 4-methylthiodiphenyl sulfide and 4,4′-bis(methylthio)diphenyl sulfide (eq 2).[2] Other examples of methylthiolation of aromatic substrates have been reported.[7]



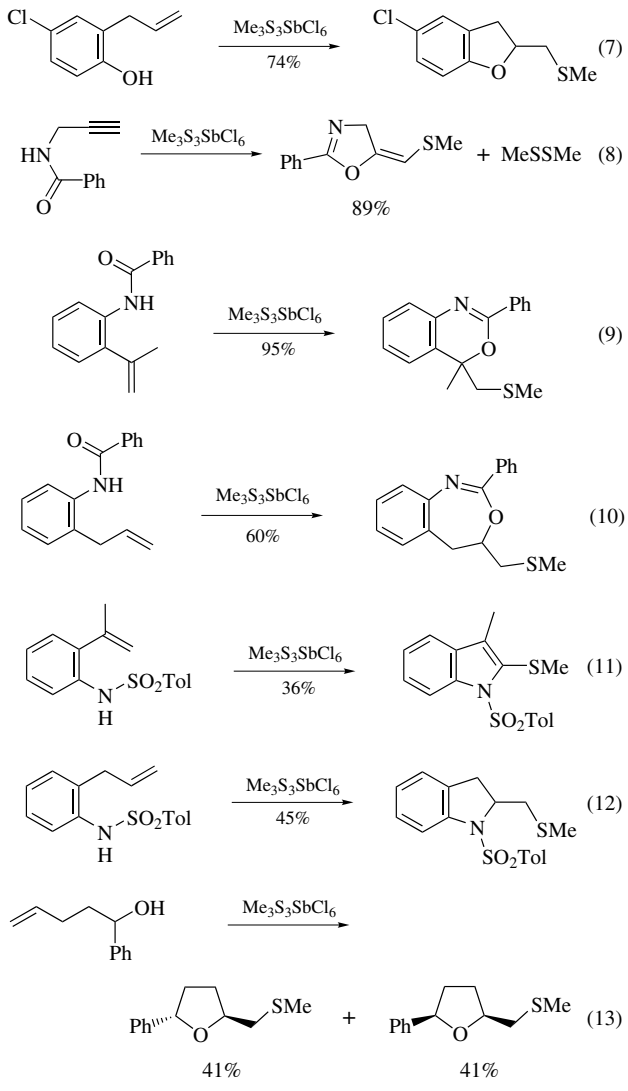


The reaction of $Me_3S_3SbCl_6$ with alkenes[8–12] and alkynes[13–16] gives thiiranium and thiirenium ions respectively. Depending on the structure of the unsaturated derivatives and reaction conditions, the three-membered ring sulfonium ions can be spectroscopically characterized or isolated as stable hexachloroantimonate salts. Some examples are shown in eqs 3–6. It is important to note the formation of only *trans,trans*-1-methylthiiranium salts from (*Z*)-alkenes[8–11] (eq 3) and the rearrangement of *cis,trans*-1-methyl-2,3-di-*t*-butylthiiranium ion to a thietanium ion (eq 4).[10,11] Dialkylacetylenes give thiirenium ions which are stable at low temperature in SO_2 solution. The presence of bulky alkyl residues makes these ions stable enough to be isolated at rt as hexachloroantimonate salts (eq 5).[14,16] Arylalkylacetylenes undergo addition of the Me_3S_3 residue to the triple bond (eq 6).[17] The characteristic reactivity of thiiranium and thiirenium ions implies attack at ring carbons by nucleophiles with ring opening.[1] Nucleophiles also attack the sulfonium sulfur;[1] however, this reaction is masked sometimes by its reversibility.





Cyclofunctionalization of Alkenes and Alkynes. The nucleophilic ring opening of thiiranium and thiirenium ions has been exploited for the synthesis of functionalized heterocycles using $Me_3S_3SbCl_6$ and suitably substituted alkenes and alkynes (eqs 7–13).[7,18–23]



1. (a) Capozzi, G., *Pure Appl. Chem.* **1987**, *59*, 989. (b) Capozzi, G.; Modena, G. In Studies in Organic Chemistry 19. Organic Sulfur Chemistry. *Theoretical and Experimental Advances*; Elsevier: New York, 1985; Chapter 5. (c) Capozzi, G.; Modena, G.; Pasquato, L.; *The Chemistry of Sulfenic Acids and Their Derivatives*; Wiley: New York, 1990; Chapter 10.
2. Tsuchida, E.; Yamamoto, K.; Nishide, H.; Yoshida, S.; Jikei, M., *Macromolecules* **1990**, *23*, 2101.
3. Capozzi, G.; Lucchini, V.; Modena, G.; Rivetti, F., *J. Chem. Soc., Perkin Trans. 2* **1975**, 900.
4. Weiss, R.; Schlierf, C., *Synthesis* **1976**, 323.
5. Capozzi, G.; DeLucchi, O.; Lucchini, V.; Modena, G., *Synthesis* **1976**, 677.
6. (a) Helmkamp, G. K.; Cassey, H. N.; Olsen, B. A.; Pettitt, D. J., *J. Org. Chem.* **1965**, *30*, 933. (b) Smallcombe, S. H.; Caserio, M. C., *J. Am. Chem. Soc.* **1971**, *93*, 5826.
7. Capozzi, G.; Lucchini, V.; Marcuzzi, F.; Modena, G., *J. Chem. Soc., Perkin Trans. 1* **1981**, 3106.
8. Capozzi, G.; DeLucchi, O.; Lucchini, V.; Modena, G., *Tetrahedron Lett.* **1975**, 2603.
9. Minkwitz, R.; Gerhard, V.; Krause, R.; Prenzel, H.; Preut, H., *Z. Anorg. Allg. Chem.* **1988**, *559*, 154 (*Chem. Abstr.* **1989**, *110*, 7620a).
10. Lucchini, V.; Modena, G.; Pasquato, L., *J. Am. Chem. Soc.* **1988**, *110*, 6900.
11. Lucchini, V.; Modena, G.; Pasquato, L., *J. Am. Chem. Soc.* **1991**, *113*, 6600.
12. Lucchini, V.; Modena, G.; Pasquato, L., *J. Chem. Soc., Chem. Commun.* **1992**, 293.
13. Capozzi, G.; DeLucchi, O.; Lucchini, V.; Modena, G., *J. Chem. Soc., Chem. Commun.* **1975**, 248.
14. Capozzi, G.; Lucchini, V.; Modena, G.; Scrimin, P., *Tetrahedron Lett.* **1977**, 911.
15. Lucchini, V.; Modena, G.; Valle, G.; Capozzi, G., *J. Org. Chem.* **1981**, *46*, 4720.
16. Capozzi, G.; Lucchini, V.; Modena, G., *Rev. Chem. Intermed.* **1979**, *2*, 347.
17. Capozzi, G.; DaCol, L.; Lucchini, V.; Modena, G., *J. Chem. Soc., Perkin Trans. 2* **1980**, 68.
18. Capozzi, G.; Caristi, C.; Gattuso, M.; Stagno D'Alcontres, G., *Tetrahedron Lett.* **1981**, *22*, 3325.
19. Capozzi, G.; Caristi, C.; Gattuso, M., *J. Chem. Soc., Perkin Trans. 1* **1984**, 255.
20. Capozzi, G.; Ottana', R.; Romeo, G.; Valle, G., *J. Chem. Res. (S)* **1986**, 200.
21. Capozzi, G.; Ottana', R.; Romeo, G., *Heterocycles* **1986**, *24*, 583.
22. Capozzi, G.; Ottana', R.; Romeo, G., *Heterocycles* **1987**, *26*, 39.
23. Capozzi, G.; Menichetti, S.; Nicastro, M.; Taddei, M., *Heterocycles* **1989**, *29*, 1703.

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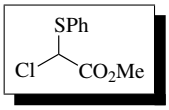
Methyl α-Chloro-α-phenylthioacetate



[85920-99-6] $C_9H_9ClO_2S$ (MW 216.70)

InChI = 1/C9H9ClO2S/c1-12-9(11)8(10)13-7-5-3-2-4-6-7/h2-6,8H,1H3

InChIKey = HHVMSWORZCJJKS-UHFFFAOYAQ

(an a^2 carbon electrophile for the introduction of methoxycarbonylmethyl and methoxycarbonylmethylidene groups by Lewis acid-catalyzed reaction with silyl enol ethers followed by a reductive or oxidative step)

Physical Data: bp 105–107 °C/18 mmHg.[1]

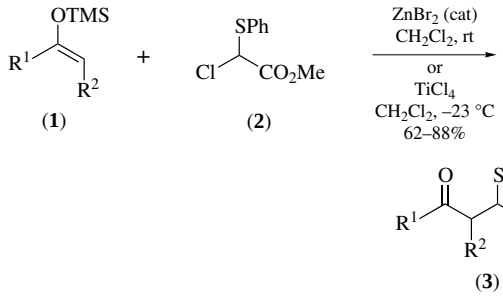
Solubility: freely sol CH_2Cl_2.

Analysis of Reagent Purity: δ ($CDCl_3$) 7.47 (5H, m), 5.57 (1H, s), and 3.77 (3H, s).

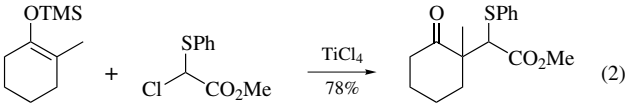
Preparative Methods: by chlorination of methyl phenylthioacetate using sulfuryl chloride[2] or *N*-chlorosuccinimide (NCS):[3,4] methyl phenylthioacetate (16.8 g) is stirred with powdered NCS (13.3 g) in CCl_4 at rt for 10 h, the mixture filtered, the filtrate evaporated, and the residue distilled using a short Vigreux column.[1]

Handling, Storage, and Precautions: generally prepared shortly before use. It is stable in the absence of water, and should be kept in a stoppered flask or sealed ampule if it is not used immediately. It is an alkylating agent, and should therefore be kept in a well-ventilated hood, with skin and eyes protected while handling it.

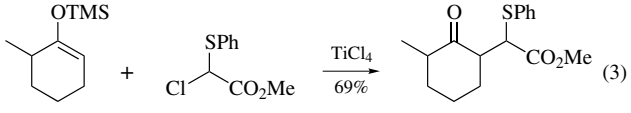
Methyl α-chloro-α-phenylthioacetate (**2**) reacts with silyl enol ethers (**1**) in the presence of Lewis acids, typically zinc bromide in catalytic quantities[3,4] or titanium(IV) chloride in stoichiometric quantities,[4] to give the 1,4-dicarbonyl products (**3**) (eq 1). The reaction is regiospecific (eqs 2 and 3),[4] and γ-selective with the silyl dienol ether (**4**) (eq 4).[3]



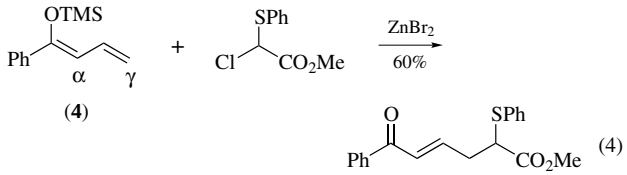
(1)



(2)



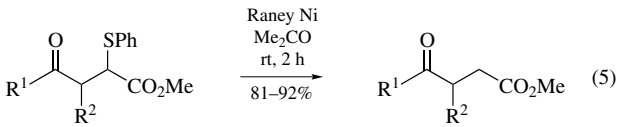
(3)



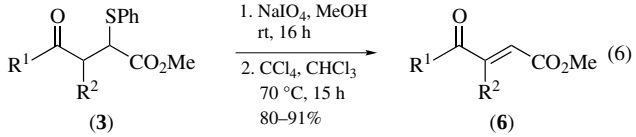
(4)

The $ZnBr_2$ reactions typically take 0.5–2 h at rt in CH_2Cl_2, and are carried out by adding the anhydrous salt to a 1:1 mixture of silyl enol ether and the chloride (**1**). The $TiCl_4$ reactions are carried out similarly, and typically take 2 h at −23 °C.

The products (**3**) can be desulfurized with Raney nickel to give overall the products (**5**) of methoxycarbonylmethylation (eq 5).[3,4] They can also be oxidized using sodium periodate to give the corresponding sulfoxides, which undergo rapid cycloelimination when there is an appropriately placed hydrogen atom to give overall the products (**6**) of methoxycarbonylmethylidenation (eq 6).[3,4]

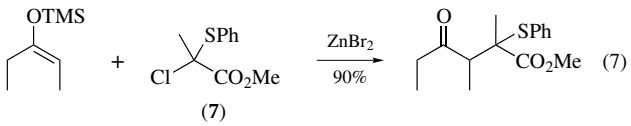


(5)

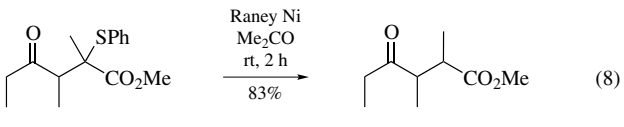


(6)

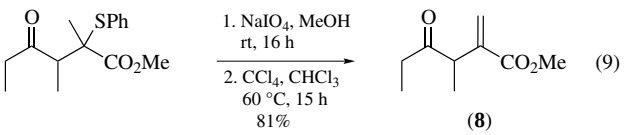
The homolog methyl 2-chloro-2-phenylthiopropanoate (**7**) can be used in similar reactions (eqs 7–9), but the oxidative desulfurization takes place towards the methyl group, giving the α-methylene ester (**8**) when R^2 is not hydrogen (eq 9).[4]



(7)



(8)



(9)

The corresponding Lewis acid-catalyzed reaction of silyl enol ethers with α-chloro-α-phenylthioketones gives furans.[5]

Related Reagents. Chloromethyl Phenyl Sulfide.

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1. Iqbal, J. Unpublished result, Cambridge, 1982.
2. Campbell, M. M.; Jigajinni, V. B.; MacLean, K. A.; Wightman, R. H., *Tetrahedron Lett.* **1980**, *21*, 3305.
3. (a) Lee, T. V.; Okonkwo, J. O., *Tetrahedron Lett.* **1983**, *24*, 323. (b) Lee, T. V.; Toczek, J., *J. Chem. Soc., Perkin Trans. 1* **1987**, 759.

4. Fleming, I.; Iqbal, J., *Tetrahedron Lett.* **1983**, *24*, 327.
5. Tanikaga, R.; Miyashita, K.; Sugihara, H.; Kaji, A., *J. Chem. Soc., Chem. Commun.* **1981**, 1106.

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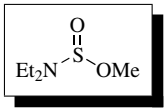
Methyl Diethylamidosulfite[1]

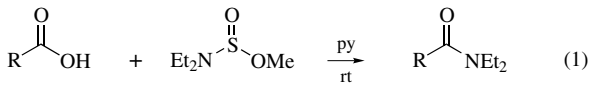


[21954-69-8] $C_5H_{13}NO_2S$ (MW 151.26)
InChI = 1/C5H13NO2S/c1-4-6(5-2)9(7)8-3/h4-5H2,1-3H3
InChIKey = DKGGSWZTFYZHQC-UHFFFAOYAT

(conversion of carboxylic acids to *N,N*-diethylamides[2])

Physical Data: bp 73–74 °C/10 mmHg.
Solubility: sol diethyl ether.
Form Supplied in: clear oil.
Analysis of Reagent Purity: titration with iodine.
Preparative Method: reaction of diethylamine and chlorosulfurous acid in diethyl ether.[1,2]
Purification: vacuum distillation.[2]
Handling, Storage, and Precautions: prolonged heating at atmospheric pressure causes decomposition with evolution of sulfur dioxide.

This reagent reacts with primary and secondary carboxylic acids in the presence of pyridine to give *N,N*-diethylamides (eq 1). The reaction is typically run at rt and requires a long reaction time (several days). In general, tertiary acids and α-amino carboxylic acids do not react.[2,3]



(1)

1. (a) Zinner, G., *Chem. Ber.* **1958**, *91*, 966. (b) Voss, M.; Blanke, E., *Justus Liebigs Ann. Chem.* **1931**, *485*, 258.
2. Takei, H.; Shimizu, H.; Hizo, M.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1925.
3. Becker, H. G. O.; Funk, K. F., *J. Prakt. Chem.* **1961**, *14*, 55.

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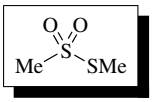
Methyl Methanethiosulfonate[1]



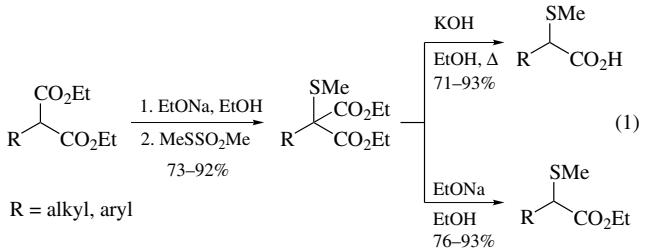
[2949-92-0] $C_2H_6O_2S_2$ (MW 126.22)
InChI = 1/C2H6O2S2/c1-5-6(2,3)4/h1-2H3
InChIKey = XYONNSVDNIRXKZ-UHFFFAOYAA

(methylsulfenylating agent with many applications;[2] reagent for the rapid and selective modification of the essential SH groups of enzymes. The MeS-protecting group is easily removed under mild conditions[3])

Alternate Name: *S*-methyl thiomethanesulfonate.
Physical Data: bp 69–71 °C/0.4 mmHg; *d* 1.227 g cm^{-3}; *n* 1.5130.
Form Supplied in: colorless oil; widely available.
Handling, Storage, and Precautions: stench; irritant. Use in a fume hood.

Introduction. Methyl methanethiosulfonate is a versatile reagent mainly used to form sulfenylated intermediates used en route to the synthesis of various interesting compounds. It is a much more reactive and effective sulfenylating agent than dimethyl disulfide or MeSCl.[4] $MeSSO_2Me$ (and its reaction products) has little odor, which makes it considerably more agreeable to work with than MeSSMe. The MeS group transferred via deprotonation of the substrate's acidic proton with a base, followed by electrophilic substitution, can serve as a protecting group,[5] an activating group for carbanion formation, or as a masked ketone or aldehyde. It can serve as a handle for subsequent transformation to various functionalities (e.g. alkene, ketone, and alkyl group) via oxidation or reduction.

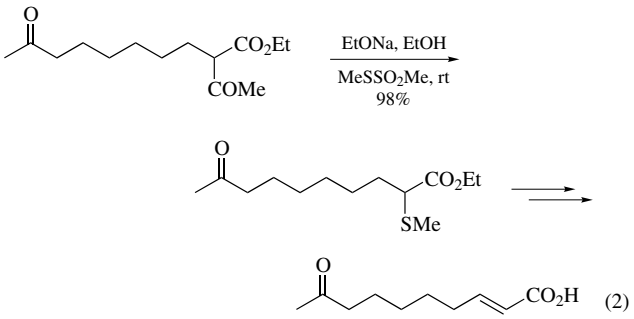
Preparation of 2-(Methylthio)alkanoic Acids and Esters and 3-Methylthio-2-alkanones. 2-(Methylthio)alkanoic acids and esters are synthesized by successive treatment of substituted malonic esters with sodium ethoxide and $MeSSO_2Me$, followed by alkaline hydrolysis which causes concurrent decarboxylation (eq 1).[6]



(1)

More conveniently, 2-(methylthio)alkanoic esters are prepared from 2-acetylalkanoates (eq 2).[7] MeSSMe cannot replace $MeSSO_2Me$ as the sulfenylating agent in this transformation. Advantages of these methods over others such as sulfenylation of an alkanoic acid and its ester or alkylation of (methylthio)acetic acid are (1) simplicity of the procedure; (2) efficiency and convenience of using inexpensive base (EtONa) and EtOH as solvent with high product yields; and (3) no bissulfenylation. Moreover, the latter

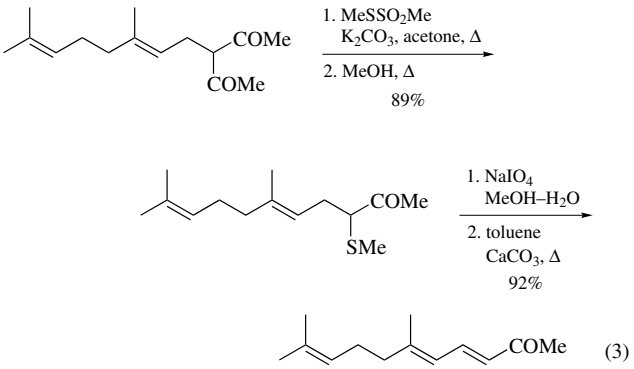
method allows direct α-sulfenylation of 2-acetylalkanoates which also contain an additional keto group, without its protection (eq 2).



(2)

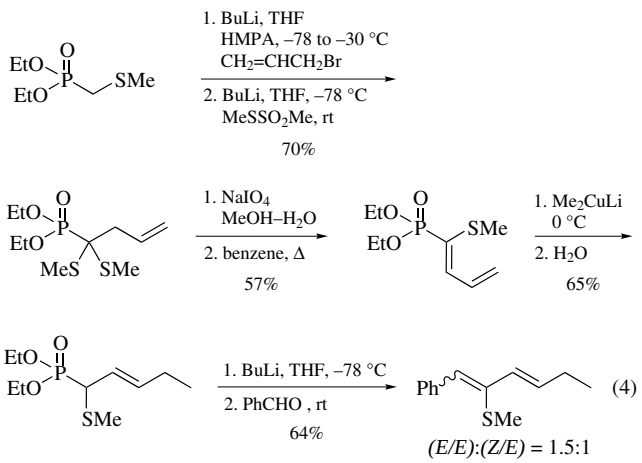
This contrasts to thiomethylation of methyl 9-oxodecanoate with MeSSMe and lithium cyclohexyl(isopropyl)amide, as reported by Trost.[8] In spite of various reaction conditions employed, Trost's procedure gives less than 30% yield of 2-methylthio-9-oxodecanoate, accompanied by bissulfenylation when the 9-oxo group is not protected. Moreover, toxic HMPA is required to obtain 86% of the sulfenylated ester even when the 9-oxo group is protected. The transformation described in eqs 1 and 2 works with $PhSSO_2Ph$ as well.

Similarly, 3-methylthio-2-alkanones are prepared by the reaction of a 3-alkyl-2,4-pentanedione with 1 mol equiv (important) of $MeSSO_2Me$ in the presence of EtONa in EtOH at rt or potassium carbonate in acetone at reflux followed by addition of MeOH and reflux. An advantage of using weaker base K_2CO_3 in this reaction is that no bissulfenylation takes place even when excess sulfenylating agent is used. The method was applied to an efficient synthesis of pseudoionone (eq 3).[9]



(3)

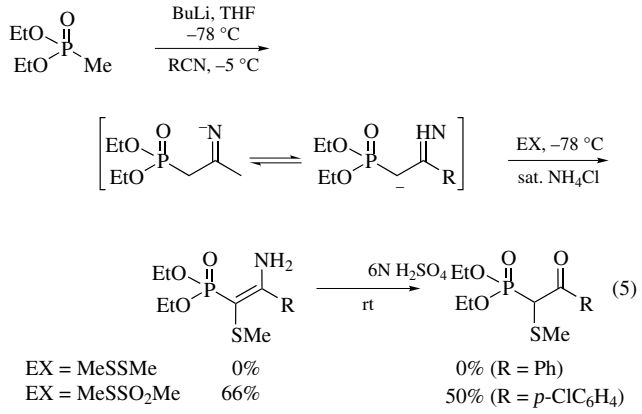
Diethyl 1-Methylthio-1(*Z*),3-butadienephosphonate. An efficient synthesis of diethyl 1-methylthio-1(*Z*),3-butadienephosphonate from diethyl methylthiomethyl phosphonate is carried out in four steps without contamination with the (*E*) geometric isomer (eq 4).[10] The methylthiobutadienephosphonate reacts smoothly with enamines. It also undergoes 1,4-addition with dialkylcuprates to yield exclusively (*E*)-alkenes. The resultant allylic phosphonates from these additions can be employed for the synthesis of 2-methylthio-substituted butadienes.



(4)

One-pot Procedure for α-Methylthio β-Keto and Enamine Phosphonates. α-Methylthio β-keto and enamine phosphonates are prepared from diethyl methylphosphonate by a one-pot procedure using a nitrile as an acyl cation equivalent, followed by treatment with $MeSSO_2Me$ as an electrophile (eq 5).[11]

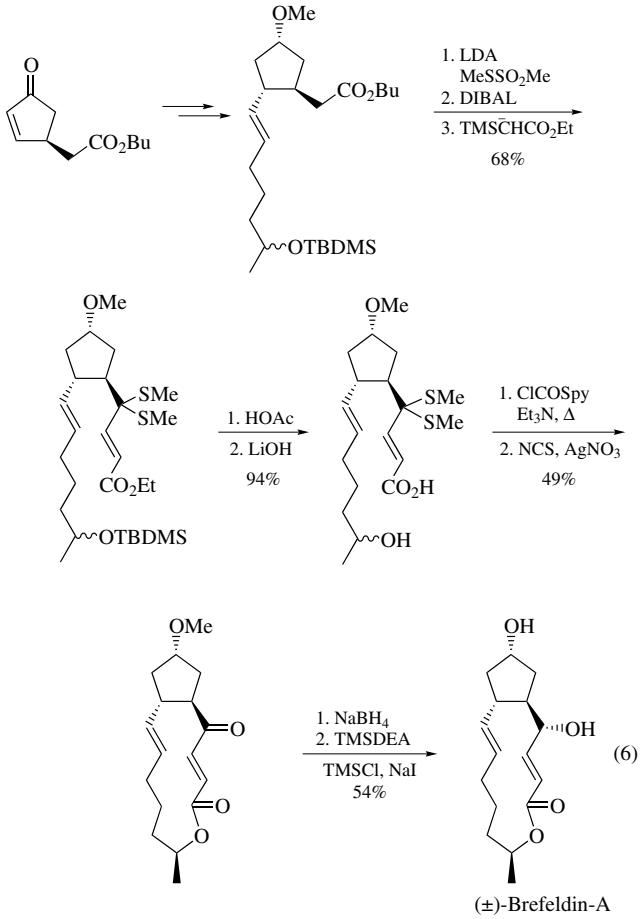
MeSSMe does not undergo this transformation due to the low reactivity of the anion toward the electrophilic sulfur moiety; however, the reaction proceeds smoothly with PhSSPh, PhSCl, and PhSeBr. Interestingly, $PhSO_2Cl$ affords α-chloro substituted phosphonates but no α-sulfonylated products.



(5)

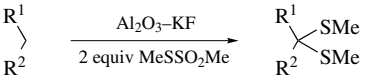
γ-Oxocrotonate Derivatives Through Bis(methylsulfenylation). An efficient sequence of reactions to transform an alkoxycarbonylmethyl group to γ-oxocrotonate via bis(methylsulfenylation) is described in a synthesis of brefeldin-A (eq 6).[12]

It is important that the methoxycarbonylmethyl group is treated twice with 1 equiv of lithium diisopropylamide and $MeSSO_2Me$ each to effect a 'one-pot' bis(methylsulfenylation). Two equiv of both LDA and $MeSSO_2Me$ cannot be present at the outset of the reaction since destruction of the reagent(s) occurs faster than the introduction of the second MeS group.[13] It is also noteworthy that a direct, one-step hydrolysis of the thioacetal group in the homologated ester to give ultimately the required γ-oxocrotonate is possible only with the dimethyl thioacetal but not with the diphenyl equivalent.[8]



(6)

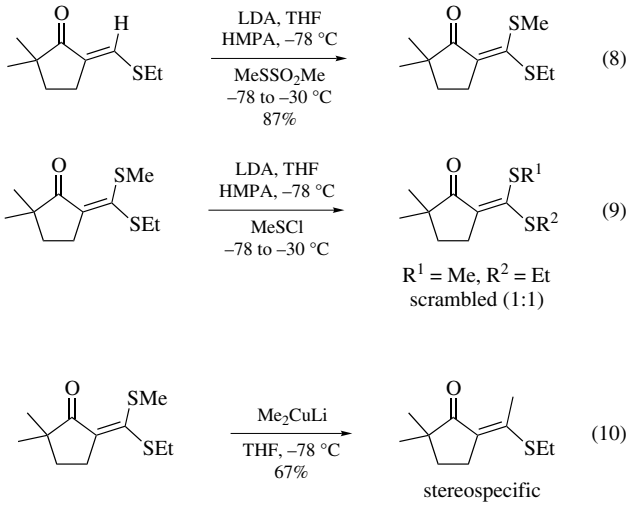
Dithioacetal Formation. Dithioacetals are prepared from activated methylene compounds with $MeSSO_2Me$ absorbed on potassium fluoride–alumina (eq 7). Microwave irradiation without solvent provides a powerful activation for this preparation. MeSCl gives only poor yields and MeSSMe does not react under these conditions.[14]



(7)

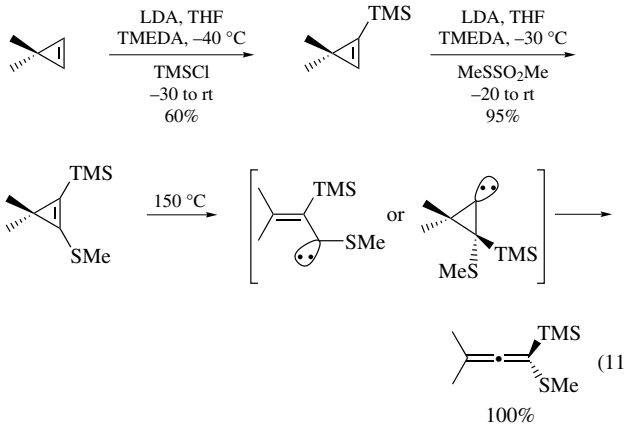
$R^1 = CO_2Et$; $R^2 = CO_2Et$, CN, Ph, MeCO (70–94%)
$R^1 = CO_2Et$; $R^2 = PO(OEt)_2$ (21%)
$R^1 = PO(OEt)_2$; $R^2 = PO(OEt)_2$ (95%)

Stereoselective Methylsulfenylation of Enones and Alkenes. An α-oxoketene dithioacetal containing two different alkylthio substituents was prepared stereoselectively from a β-alkylthio-α,β-enone via treatment with LDA and $MeSSO_2Me$ in THF–HMPA (eq 8).[15] Use of MeSCl in this reaction yields a 1:1 mixture of the stereoisomers, possibly due to isomerization of the double bond geometry by the chloride ion formed in the reaction (eq 9). The reaction of the α-oxoketene dithioacetal with organocuprate reagents proceeds stereospecifically (eq 10), in that the alkylthio substituent *syn* to the ketone carbonyl is replaced by the cuprate ligand in all cases studied.



1-(Methylthio)-substituted cyclopropenes are easily prepared by electrophilic substitution of the protected monolithiated 3,3-dimethylcyclopropenes. Upon heating or under photolysis, the substituted cyclopropenes rearrange to allenes via possible mechanisms described in eq 11. Both the substituted cyclopropenes and rearranged products provide an interesting combination of functionalities, which make them potentially useful building blocks in organic synthesis.[16]

Unsymmetrical Disulfides. Unsymmetrical aryl and alkyl disulfides are prepared from silyl sulfides and $MeSSO_2Me$ in $CHCl_3$ at 60 °C.[17] Methyl 2- and 4-pyridyl disulfide are prepared conveniently from 2- and 4-thiopyridone and $MeSSO_2Me$ in the presence of NaOH in H_2O in excellent yields.[18]



Related Reagents. Dimethyl Disulfide; Methylsulfenyl Trifluoromethanesulfonate; Methyl *p*-Toluenethiosulfonate.

1. Trost, B. M., *Chem. Rev.* **1978**, *78*, 363.
2. Laszlo, P.; Mathy, A., *J. Org. Chem.* **1984**, *49*, 2281.
3. (a) Smith, D. J.; Maggio, E. T.; Kenyon, G. L., *Biochemistry* **1975**, *14*, 766. (b) Welches, W. R.; Baldwin, T. O., *Biochemistry* **1981**, *20*, 512.
4. (a) Scholz, D., *Synthesis* **1983**, 944. (methylsulfenylation of cyclic ketones) (b) Wladislaw, B.; Marzorati, L.; Ebeling, G., *Phosphorus Sulfur Silicon* **1990**, *48*, 163 (methylsulfenylation of *o*-, *m*-, *p*-substituted benzylsulfones). See also Ref. 14.

5. Shah, N. V.; Cama, L. D., *Hetrocycles* **1987**, *25*, 221. (MeS group is used for protection of the azetidinone NH; the protected *N*-SMe is acid stable).
6. Ogura, K.; Itoh, H.; Morita, T.; Sanada, K.; Iida, H., *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1216.
7. Ogura, K.; Sanada, K.; Takahashi, K.; Iida, H., *Tetrahedron Lett.* **1982**, *23*, 4035.
8. Trost, B. M.; Salzmann, T. N.; Hiroi, K., *J. Am. Chem. Soc.* **1976**, *98*, 4887.
9. Ogura, K.; Sanada, K.; Takahashi, K.; Iida, H., *Phosphorus Sulfur* Silicon **1983**, *16*, 83.
10. Martin, S. F.; Garrison, P. J., *Synthesis* **1982**, 394.
11. Lee, K.; Oh, D. Y., *Synth. Commun.* **1991**, *21*, 279.
12. (a) Le Drian, C.; Greene, A. E., *J. Am. Chem. Soc.* **1982**, *104*, 5473. (b) Greene, A. E.; Le Drian, C.; Crabbé, P., *J. Org. Chem.* **1980**, *45*, 2713.
13. In contrast to bis(phenylsulfenylation). See (a) Ref. 8; also (b) Trost, B. M.; Massiot, G. S., *J. Am. Chem. Soc.* **1977**, *99*, 4405;(c) Trost, B. M.; Mao, M. K. T., *Tetrahedron Lett.* **1980**, *21*, 3523.
14. Villemin, D.; Ben Alloum, A.; Thibault-Starzyk, F., *Synth. Commun.* **1992**, *22*, 1359.
15. Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. R.; Kastner, M. E., *J. Am. Chem. Soc.* **1985**, *107*, 4679.
16. Kirms, M. A.; Primke, H.; Stohlmeier, M.; De Meijere, A., *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 462.
17. Capozzi, G.; Capperucci, A.; Degl'Innocenti, A.; Del Duce, R.; Menichetti, S., *Tetrahedron Lett.* **1989**, *30*, 2995.
18. Kitson, T. M.; Loomes, K. M., *Anal. Biochem.* **1985**, *146*, 429.

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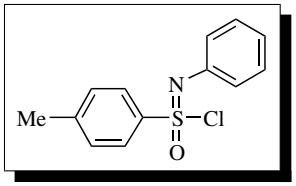
4-Methyl-*N*-phenylbenzene Sulfonimidoyl Chloride



[123552-85-2] $C_{13}H_{12}ClNOS$ (MW 265.76)

InChI = 1/C13H12ClNOS/c1-11-7-9-13(10-8-11)17(14,16)15-12-5-3-2-4-6-12/h2-10H,1H3

InChIKey = IZVYUBSVHAMQJJ-UHFFFAOYAG

Physical Data: not reported.

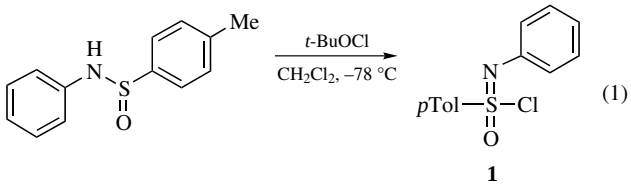
Solubility: CH_2Cl_2, polar organic solvents.

Form Supplied in: yellow solid, prepared fresh.

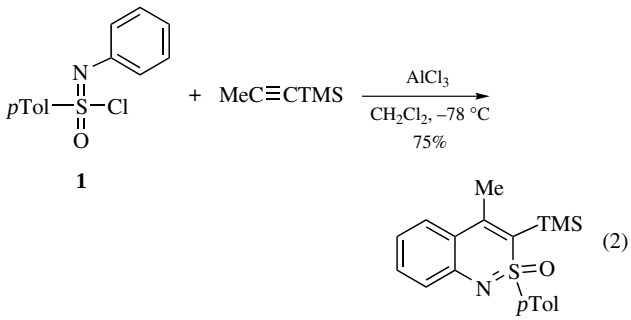
Preparative Methods: the title sulfonimidoyl chloride (**1**) is prepared by the reaction of the corresponding sulfinamide with *tert*-butyl hypochlorite in dichloromethane at −78 °C (eq 1).[1] Simple evaporation of the solvent and excess hypochlorite produces a reagent of sufficient quality for most current applications. The reagent can be generated and used in situ.

Purity: not reported, although recrystallization should be possible.

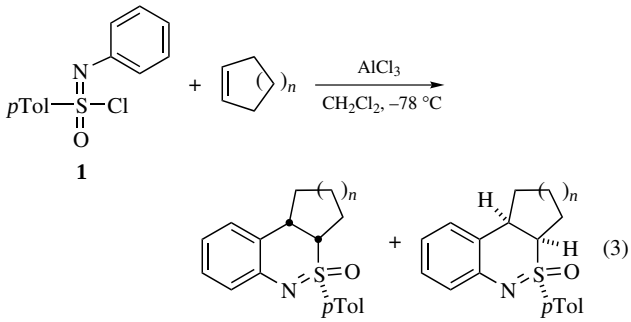
Handling, Storage, and Precautions: the reagent is not stable for long periods of time and should be prepared as needed. It is subject to hydrolysis and reaction with other nucleophiles such as alcohols. In the absence of a reaction partner, it will decompose in the presence of Lewis acids, generally producing an intensely blue-colored substance whose structure is unknown.



Reaction with Alkynes. Treatment of a dichloromethane solution of the sulfonimidoyl chloride (**1**) with a Lewis acid in the presence of an alkyne affords 2,1-benzothiazines in good-to-excellent yields with high Markownikoff regioselectivity (eq 2).[2] Finely powdered aluminum chloride is the Lewis acid of choice for this reaction, though titanium chloride works reasonably well.

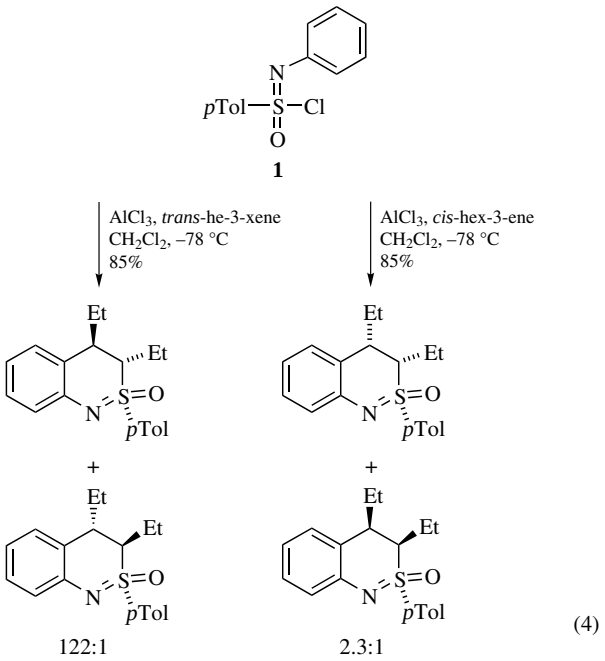


Reaction with Alkenes. The reaction of the title reagent (**1**) with alkenes mediated by Lewis acids produces results similar to those observed with alkynes, though with complications created by the formation of stereogenic centers.[3] With cyclic alkenes, adducts are produced in excellent yields and with generally poor diastereoselection, with the exception of cyclohexene, which leads to two products in a ratio of 25:1 (eq 3).



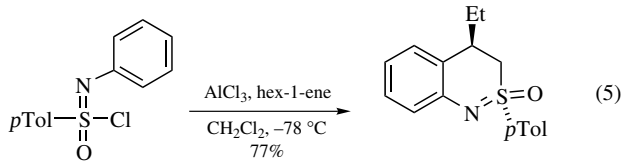
n = 1, 81%, 5:1
n = 2, 91%, 25:1
n = 3, 70%, 2.4:1
n = 4, 76%, 2.1:1

cis- and *trans*-hex-3-ene lead to unique sets of adducts, with no stereochemical crossover being observed (eq 4). Furthermore, the reaction with *trans*-hex-3-ene proceeds with excellent diastereoselectivity.

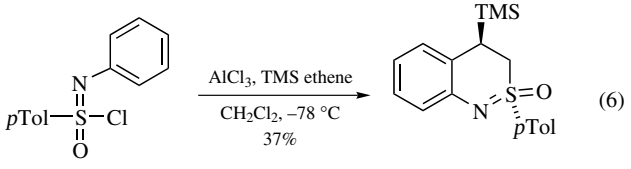


(4)

More extensive studies on the effect of alkene substitution on the course of the reaction have been reported.[4] For terminal alkenes, yields are good but diastereoselection is poor as exemplified by the reaction of hex-1-ene (eq 5). With trimethylsilylethene, the yield dropped to 35% but the diastereoselection was 10:1 (eq 6). This process could be improved to afford a 61% yield of benzothiazines in a 9.2:1 ratio when tin tetrachloride was used as the Lewis acid.[5]

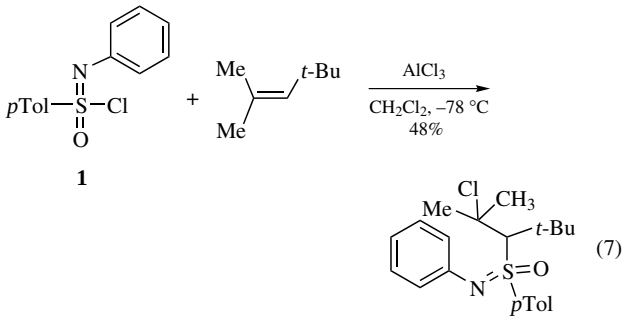


(5)



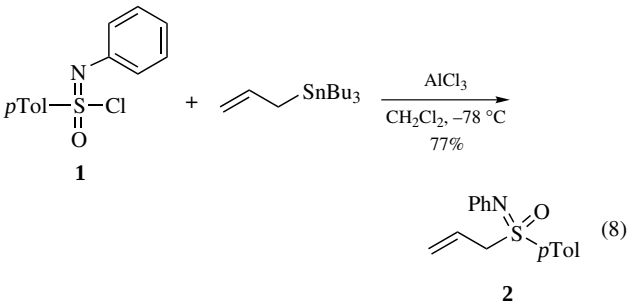
(6)

1,1-Disubstituted alkenes reacted with (**1**) to give fair-to-good yields of benzothiazines with generally low diastereoselectivity. Side products resulting from carbocationic rearrangements were observed to a small extent. Such rearrangement products can often dominate the reaction if the alkenes are sufficiently bulky. For example, the reaction of (**1**) with 2,4,4-trimethylpent-2-ene in the presence of aluminum chloride afforded only a chlorosulfoximine in 48% yield as a single isomer under conditions which normally produce benzothiazines (eq 7).



(7)

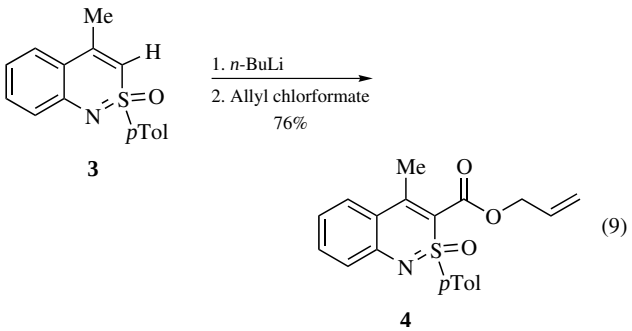
Interestingly, when (**1**) reacted with allyltributyltin, no benzothiazine was formed at all. Instead, the allyl sulfoximine (**2**) was produced in 77% yield (eq 8).[6] Although studies of the alkylation of the anion of **2** did not demonstrate high degrees of diastereoselection, subsequent work with allylic sulfoximines demonstrated that such reagents could be quite useful in asymmetric synthesis.[7]



(8)

Benzothiazine Chemistry. The benzothiazines formed from the title sulfonimidoyl chloride are potentially useful as templates for the development of new chemistry. Examples are provided below.

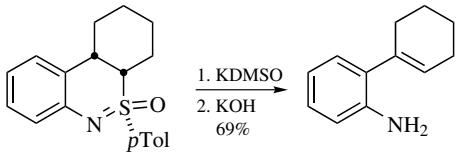
Deprotonation and Alkylation. One report demonstrates that benzothiazines derived from the reaction of (**1**) with alkynes can be deprotonated with **BuLi** and alkylated with various electrophiles.[8] For example, treatment of (**3**) with *n*-BuLi followed by reaction with allyl chloroformate afforded the ester (**4**) in 76% yield (eq 9). Other electrophiles could also be used. Aldehydes afforded adducts in good yields but with only low levels of diastereoselectivity.



(9)

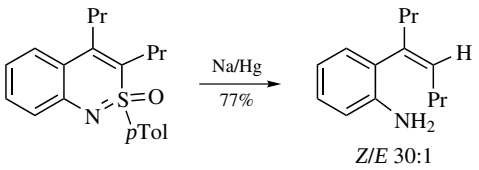
Synthesis of 2-Alkenylanilines. Three methods have been reported for the conversion of benzothiazines into 2-alkenylanilines. In the first, benzothiazine derived from the reaction of **1** with alkenes were treated with potassium dimsylate (KDMSO) and

subsequently saponified to produce the target anilines (eq 10).[9] With alkenes able to accommodate *E*/*Z* isomers, these were generally formed with little-to-no stereoselectivity.



(10)

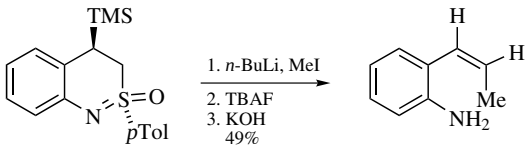
A different approach to 2-alkenylanilines makes use of benzothiazines derived from the reaction of **1** with alkynes. Reduction of these compounds with sodium amalgam leads directly to the product anilines.[10] Interestingly, for those systems examined which could produce geometrical isomers, these were formed with good-to-excellent stereoselectivity, in all cases favoring the *Z*-isomers (eq 11).



(11)

Z/*E* 30:1

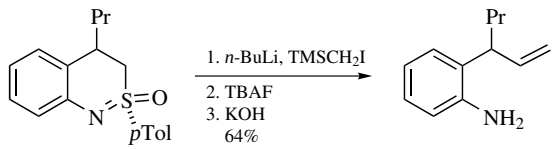
The last 2-alkenylaniline synthesis begins with the benzothiazines formed from the reaction of (**1**) with trimethylsilylethene.[5] Deprotonation of the benzothiazine with BuLi and subsequent alkylation afforded the corresponding alkylation products, with moderate diastereoselectivity in most cases. Treatment of these alkylation products with tetrabutylammonium fluoride (TBAF) afforded sulfinamides which could be hydrolyzed to the corresponding anilines (eq 12). Interestingly, the desilylation step generally favored the formation of *Z*-alkenes, with variable stereoselectivity. The saponification step resulted in some loss of the stereochemical integrity of the double bond, though *Z*-isomers were still produced relatively selectively.



(12)

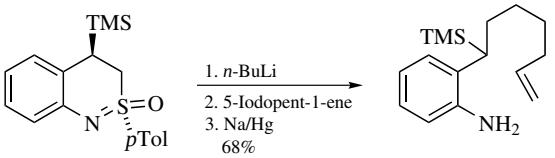
Z/*E* 11.4:1

Synthesis of 2-Allylanilines. The synthesis of 2-allylanilines has been reported to proceed from benzothiazines derived from the reaction of (**1**) with alkenes.[11] Alkylation of the corresponding organolithium compounds using iodomethyltrimethylsilane as the electrophile followed by treatment with fluoride affords 2-allylsulfinamides which can be hydrolyzed to the corresponding anilines (eq 13).



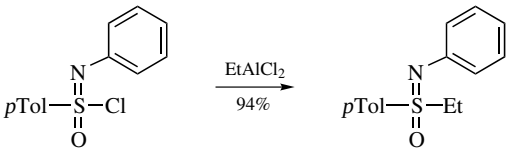
(13)

Synthesis of 2-Alkylanilines. The preparation of 2-alkylanilines is related to the reduction procedure for the synthesis of 2-alkenylanilines.[12] The benzothiazines used are those derived from the reaction of (**1**) with alkenes. Direct reduction with sodium amalgam affords the anilines directly. Modifications of the benzothiazines can precede the step involving sulfur extrusion (eq 14).



(14)

Reaction with Ethylaluminum Dichloride. A new sulfoximine synthesis using (**1**) and related compounds has been reported.[13] The reaction of (**1**) with ethylaluminum dichloride in dichloromethane at −78°C afforded the sulfoximine (**5**) in 94% yield (eq 15). Other sulfonimidoyl chlorides produced fair-to-excellent yields of the corresponding *S*-ethyl sulfoximines.



(15)

1 **5**

Related Reagents. The most closely related reagent to (**1**) is *N*-phenylbenzenesulfonimidoyl chloride.[14] It should be therefore be anticipated that reactions of (**1**) with primary and secondary amines and with metal alkoxides and particularly phenoxides should proceed uneventfully to produce sulfondimidamides and sulfonimidates. Further, the reaction with fluoride sources such as sodium fluoride should produce the corresponding sulfonimidoyl fluorides.[15] Other congeners of (**1**) are known,[13] and their chemistry is anticipated to be closely related to that described herein.

1. Johnson, C. R.; Wambsgans, A., *J. Org. Chem.* **1979**, *44*, 2278.
2. Harmata, M.; Schlemper, E. O., *Tetrahedron Lett.* **1987**, *28*, 5997.
3. Harmata, M.; Claassen II, R. J.; Barnes, C. L., *J. Org. Chem.* **1991**, *56*, 5059.
4. Harmata, M.; Kahraman, M., *J. Org. Chem.* **1998**, *63*, 6845.
5. Harmata, M.; Kahraman, M.; Jones, D. E.; Pavri, N.; Weatherwax, S. E., *Tetrahedron* **1998**, *54*, 9995.
6. Harmata, M.; Claassen II, R. J., *Tetrahedron Lett.* **1991**, *32*, 6497.
7. (a) Pyne, S. G., *Sulfur Reports* **1999**, *21*, 281. (b) Reggelin, M.; Zur, Z., *Synthesis* **2000**, 1.
8. Harmata, M., *Tetrahedron Lett.* **1988**, *29*, 5229.
9. Harmata, M.; Herron, B. F., *Tetrahedron* **1991**, *47*, 8855.
10. Harmata, M.; Kahraman, M., *Synthesis* **1995**, 713.
11. Harmata, M.; Jones, D. E., *Tetrahedron Lett.* **1995**, *36*, 4769.
12. Harmata, M.; Kahraman, M., *Synthesis* **1994**, 142.
13. Harmata, M., *Tetrahedron Lett.* **1989**, *30*, 437.
14. Johnson, C. R.; Jonsson, E. U.; Bacon, C. C., *J. Org. Chem.* **1979**, *44*, 2055.
15. Johnson, C. R.; Kostaki, G. B.; Cantillo, J. H.; Meanwell, N. A.; Reinhard, M. F. D.; Zeller, J. R.; Vonk, G. P., *J. Org. Chem.* **1983**, *48*, 1.

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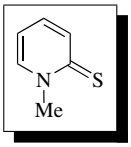
1-Methyl-2(1*H*)-pyridinethione



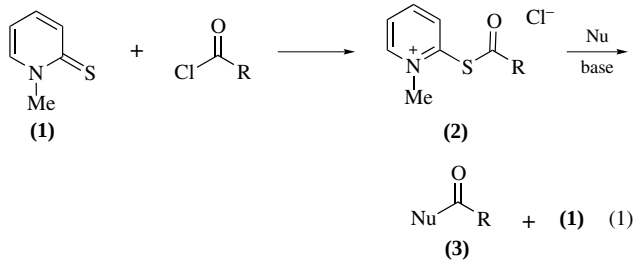
[2044-27-1] C_6H_7NS (MW 125.21)
InChI = 1/C6H7NS/c1-7-5-3-2-4-6(7)8/h2-5H,1H3
InChIKey = UHOAUPKGWPQNDM-UHFFFAOYAE

(sulfur transfer; carbonyl activation)

Physical Data: pale yellow leaflets; mp 89–90 °C.
Preparative Method: prepared in 80–90% yield from commercially available 1-methyl-2(1*H*)-pyridone by treatment with phosphorus(III) iodide at 130 °C for 4–5 h.
Purification: crystallization from water.[1,2]

Introduction. The reactivity of 1-alkyl-2(1*H*)-pyridone (and -pyridinethione) derivatives has been studied extensively by Tomisawa.[3]

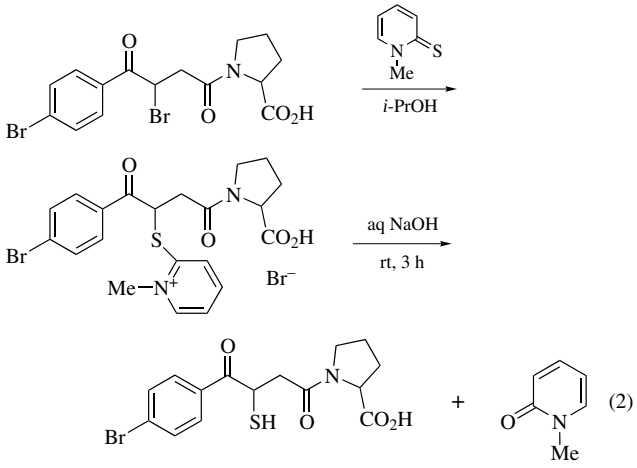
Carbonyl Activation. The title reagent (**1**) reacts with acyl chlorides to produce 2-acylthio-1-methylpyridinium salts (**2**) as stable hygroscopic solids (eq 1). These may then be treated with a variety of oxygen and nitrogen nucleophiles in the presence of base to effect transfer of the acyl group to the nucleophilic species to produce (**3**) and regenerate (**1**).[4]



(1)

R = Ph, Me, *i*-Pr, OEt; Nu = primary amines, phenols, carboxylic acids

Sulfur Transfer. The reagent has been used as a method of producing thiols from halides by alkylation on sulfur followed by hydrolysis.[5] The initial alkylation proceeds best with activated halides such as benzylic halides or α-halo carbonyl compounds, although the conversion of bromocyclohexane to the corresponding thiol occurs in 70% yield. An example (eq 2) shows the compatibility and mildness of the reagent.[6] No β-elimination product was reported.



(2)

1. Gutbier, A., *Chem. Ber.* **1900**, *33*, 3358.
2. Tomisawa, H.; Wang, C. H., *Chem. Pharm. Bull.* **1973**, *21*, 2590.
3. Tomisawa, H.; Wang, C. H., *Chem. Pharm. Bull.* **1973**, *21*, 2607 and previous papers in the series.
4. Sakakibara, T.; Watabe, Y.; Yamada, M.; Sudoh, R., *Bull. Chem. Soc. Jpn.* **1988**, *61*, 247.
5. Yamada, M.; Sotoya, K.; Sakakibara, T.; Takamoto, T.; Sudoh, R., *J. Org. Chem.* **1977**, *42*, 2180.
6. McEvoy, F. J.; Lai, F. M.; Albright, J. D., *J. Med. Chem.* **1983**, *26*, 381.

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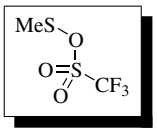
Methylsulfenyl Trifluoromethanesulfonate



[59259-48-2] $C_2H_3F_3O_3S_2$ (MW 196.19)
InChI = 1/C2H3F3O3S2/c1-9-8-10(6,7)2(3,4)5/h1H3
InChIKey = IQZYXMDOZOUMPP-UHFFFAOYAB

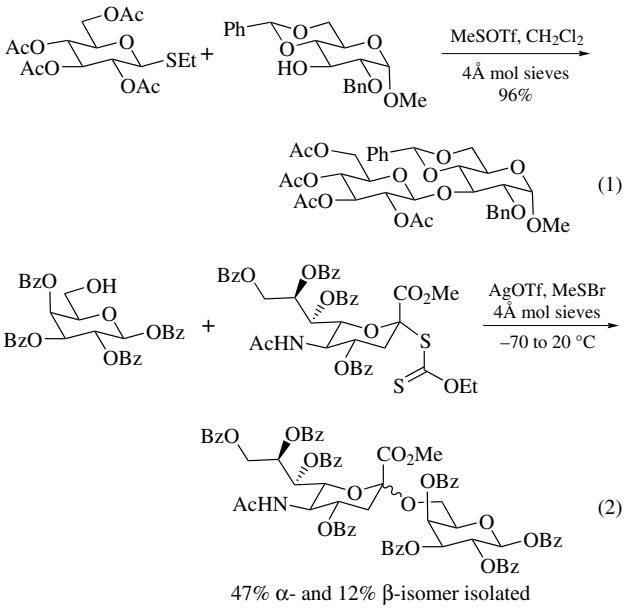
(activator for formation of glycosidic linkages)

Solubility: prepared and used in 1,2-dichloroethane,[1] acetonitrile, or CH_2Cl_2.[1,2]
Form Supplied in: prepared and utilized in situ; no characterization is reported and the compound is not commercially available from the main chemical suppliers.
Preparative Methods: prepared by injecting methylsulfenyl bromide into a light-protected flask containing silver(I) trifluoromethanesulfonate dispersed in dry 1,2-dichloroethane. The resulting supernatant liquid is removed by syringe from the precipitated solids and utilized immediately. Alternatively, the reagent may be generated in situ by addition of methanesulfenyl bromide to a mixture of substrates and silver triflate in the presence of powdered 4Å molecular sieves.

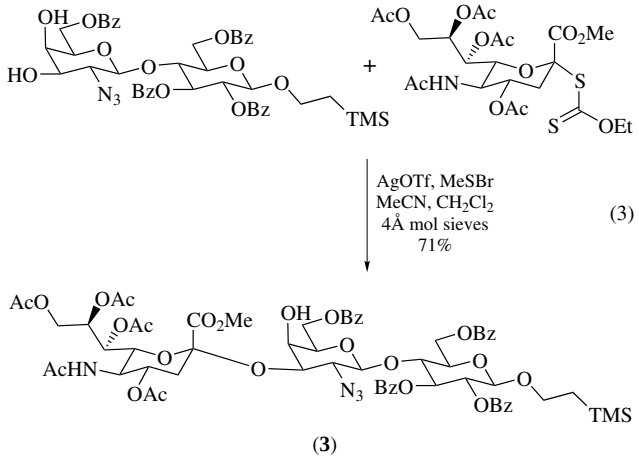
Methylsulfenyl trifluoromethanesulfonate (**1**) is an activator in the thioglycoside-mediated formation of glycosidic linkages.[1–4] (**1**) mediates 1,2-*trans* glycosidation of thioglycosides (**2**) (eq 1) by providing a superior source of the sulfenyl cation; in the absence of silver triflate, sulfenyl bromides are not glycosidation mediators.[1]

Sialosides may be prepared efficiently using (**1**) (eq 2).[3,4] The high reactivity of (**1**) allows reaction at low temperature, which is essential to minimize side reactions. Trisaccharides may also be

prepared in high yield by a similar method.[5] In these reactions, the use of a hindered amine base (such as diisopropylamine) prevents the formation of methylthioacetamides.



The same amine-modified activation process allows preparation of intermediates (**3**) crucial to the synthesis of highly complex ganglioside lactones such as GM_3 (eq 3).[6]



1. Dasgupta, F.; Garegg, P., *J. Carbohydr. Res.* **1988**, *177*, C13.
2. Dasgupta, F.; Garegg, P., *J. Carbohydr. Res.* **1990**, *202*, 225.
3. Birberg, W.; Löhn, H., *Tetrahedron Lett.* **1991**, *32*, 7453.
4. Birberg, W.; Löhn, H., *Tetrahedron Lett.* **1991**, *32*, 7457.
5. Löhn, H.; Stenvall, K., *Tetrahedron Lett.* **1992**, *33*, 115.
6. Ray, A. K.; Nilsson, U.; Magnusson, G., *J. Am. Chem. Soc.* **1992**, *114*, 2256.

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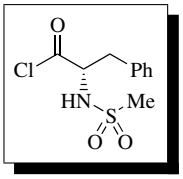
(+)-(*S*)-*N*-Methylsulfonylphenylalanyl Chloride



[63640-54-0] $C_{10}H_{12}ClNO_3S$ (MW 261.75)

InChI = 1/C10H12ClNO3S/c1-16(14,15)12-9(10(11)13)7-8-5-3-2-4-6-8/h2-6,9,12H,7H2,1H3/t9-/m0/s1

InChIKey = AKXYQEYWBQEDKN-VIFPVBQEBV

(chiral reagent for the resolution of racemic alcohols via separation of the corresponding diastereomeric esters[1])

Physical Data: mp 84–85 °C; $[\alpha]_D^{20}$ +4.3° (*c* 1.6, THF).

Solubility: readily sol THF, benzene, ether.

Form Supplied in: pale yellow needles; not available commercially.

Preparative Method: prepared from (*S*)-phenylalanine by reaction with methanesulfonyl chloride, followed by phosphorus(V) chloride.[1b]

Purification: the crude compound can be recrystallized from hexane/ether.

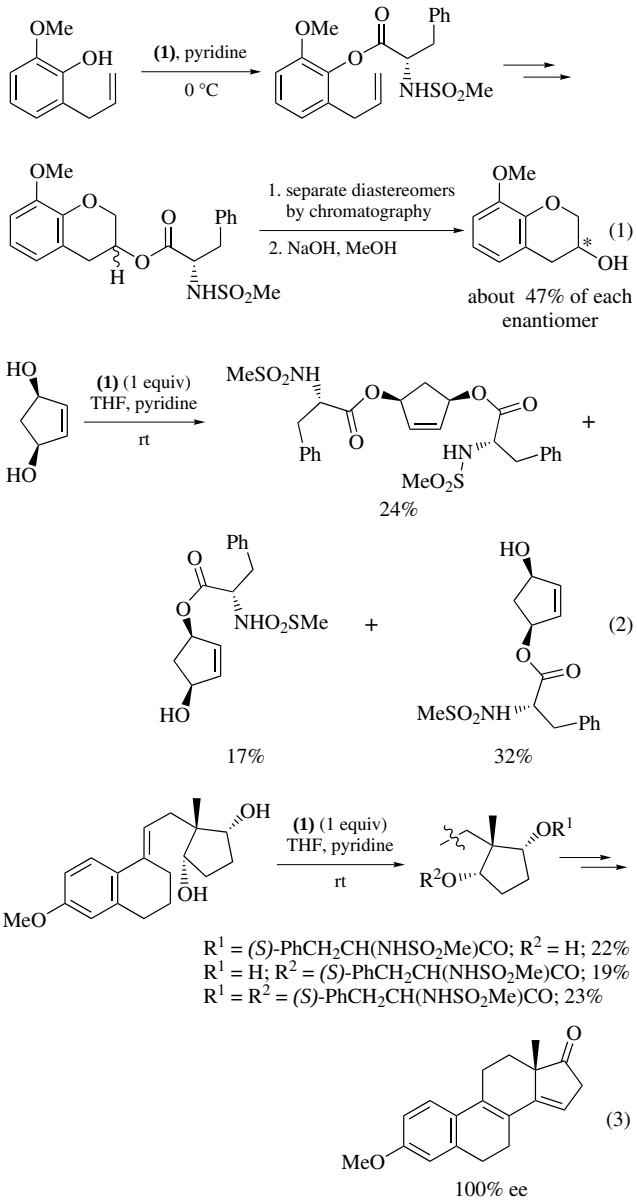
Handling, Storage, and Precautions: best if prepared immediately prior to use. Can be stored at 0 °C under nitrogen for several days without appreciable decomposition.

Introduction. Enantiomerically pure alcohols can frequently be obtained by physical separation of the diastereomeric esters prepared from the racemic alcohols and chiral acids.[2] Chiral acids that have been successfully employed for this purpose and are available in either enantiomeric form include ω-camphanic acid[3] and the monomethyl ester of diacetyltartaric acid.[4] No reagent can be considered generally applicable to all alcohols, since the ease of separation of the diastereomeric esters frequently depends on their crystallinity and/or chromatographic properties. A successful resolution is frequently the result of multiple trials and errors with a variety of acids.

***N*-Sulfonylated α-Amino Acids.** *N*-Protected derivatives of the natural α-amino acids offer a wide range of potential derivatizing agents.[5] Particularly useful are *N*-arylsulfonyl-α-amino acids,[6] many of which are commercially available and produce crystalline ester mixtures from which pure diastereomers can often be isolated by recrystallization. *N*-Methylsulfonyl-α-amino acids or the corresponding acid chlorides are generally not commercially available, but in some cases have been shown to be superior to the corresponding *N*-tosyl derivatives (eq 1).[1b,7]

N-Methylsulfonylphenylalanyl chloride (**1**) is particularly useful in the derivatization of *meso*-diols. Mixtures of diastereomeric monoesters can be obtained, from which pure diastereomers are usually isolated by fractional recrystallization and/or chromatography. Chemical transformation of the free hydroxy group, followed by removal of the chiral auxiliary, allows the selective transformation of each prochiral hydroxy group. Isolation of the other

diastereomeric ester from the mother liquors, followed by a series of protection–deprotection steps, provides the flexibility of converting 100% of the *meso*-material into one single enantiomer of the product. Alternatively, by rearranging the order of the chemical transformations, both enantiomers of the product can be obtained (eqs 2 and 3).[1,8]



1. (a) Terashima, S.; Yamada, S., *Tetrahedron Lett.* **1977**, 1001. (b) Nara, M.; Terashima, S.; Yamada, S., *Tetrahedron* **1980**, *36*, 3161.
2. *Enantiomers, Racemates and Resolutions*; Jacques, J.; Collet, A.; Wilen, S. H., Eds.; Wiley: New York, 1981; p 332.
3. Wilen, S. H.; Collet, A.; Jacques, J., *Tetrahedron* **1977**, *33*, 2725.
4. Hübner, M.; Ponsold, K.; Siemann, H. J.; Schwartz, S., *Z. Chem.* **1968**, *8*, 380.
5. Hashimoto, S.; Kase, S.; Shinoda, T.; Ikegami, S., *Chem. Lett.* **1989**, 1063.
6. (a) Jermyn, M. A., *Aust. J. Chem.* **1967**, *20*, 2283. (b) Halpern, B.; Westley, J. W., *Aust. J. Chem.* **1966**, *19*, 1533.
7. Kawamura, K.; Ohta, T.; Otani, G., *Chem. Pharm. Bull.* **1990**, *38*, 2088.
8. Nara, M.; Terashima, S.; Yamada, S., *Tetrahedron* **1980**, *36*, 3171.

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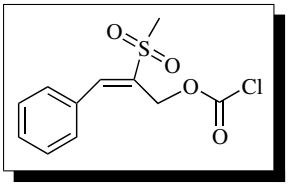
2-Methylsulfonyl-3-phenyl-1-prop-2-enyl Chloroformate



[252668-49-8] $C_{11}H_{11}ClO_4S$ (MW 274.72)

InChI = 1/C11H11ClO4S/c1-17(14,15)10(8-16-11(12)13)7-9-5-3-2-4-6-9/h2-7H,8H2,1H3

InChIKey = OAPIEQWHMLVMLO-UHFFFAOYAK

(reagent used for the introduction of a protecting group for amines)

Alternate Name: Mspoc-Cl.

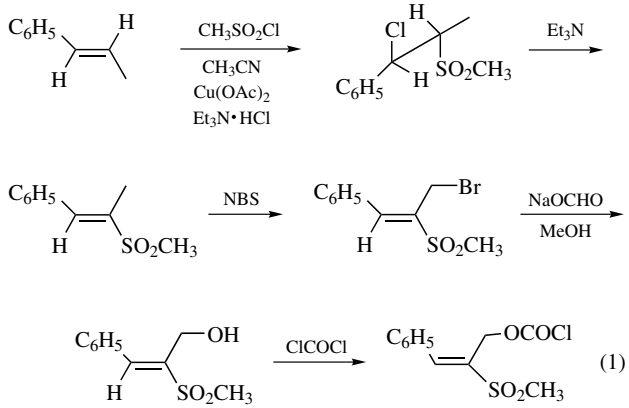
Physical Data: mp 118–120 °C, colorless crystals.[1]

Solubility: soluble in CH_2Cl_2 and $CHCl_3$; insoluble in hexanes.

Purity: recrystallized from CH_2Cl_2/hexanes.

Analysis of Reagent Purity: ^{1}H NMR, IR, elemental analysis.[1]

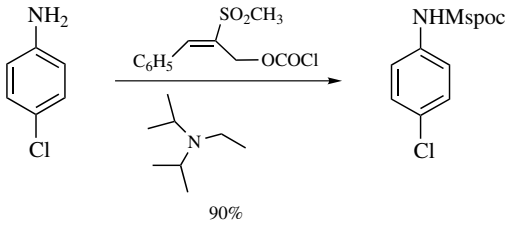
Preparative Methods: the title reagent is prepared by the reaction of 2-(methylsulfonyl)-3-phenyl-2-propenyl alcohol and phosgene (eq 1).[1] The alcohol is obtained from the corresponding allylic bromide[2] by formate-catalyzed hydrolysis.[3] The synthesis of the bromide involves the $Cu(OAc)_2$-catalyzed addition of methanesulfonyl chloride to β-methylstyrene followed by elimination of hydrogen chloride and subsequent free radical bromination of the methyl group (eq 1).[2]



Handling, Storage, and Precautions: relatively stable reagent, but moisture sensitive and best when freshly recrystallized before use. Used in a well-ventilated fume hood.

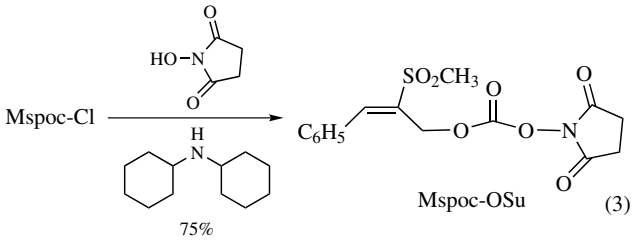
Protecting Group for Amines. 2-Methylsulfonyl-3-phenyl-1-prop-2-enyl chloroformate (Mspoc-Cl) has been introduced as an effective amino protecting group, particularly useful for peptide

synthesis. This group is more stable than the 2-*tert*-butylsulfonyl-2-propenoxy carbonyl (Bspoc) residue,[4] and avoids the problem of premature deprotection seen with Bspoc protected amines in peptide synthesis.[4] The Mspoc group can be introduced by simply treating the amine with the chloroformate in the presence of a base (eq 2).[1]



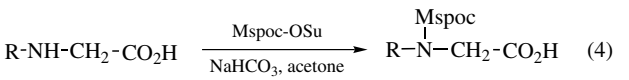
(2)

Mspoc-Cl has also been transformed into the *N*-hydroxycarbonate (Mspoc-OSu), which subsequently may be used for the protection of amino acids (eq 3).[1]



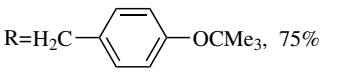
(3)

Various *N*-Mspoc protected amino acids have been synthesized using the Mspoc-OSu reagent (eq 4).[1]

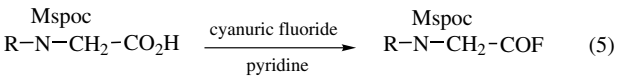


(4)

R = H, 84%
R = Bn, 82%

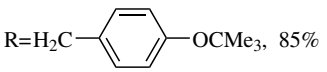


The Mspoc protected amino acids can be converted to their respective acyl fluorides[5,6] by treatment with cyanuric fluoride and pyridine (eq 5). The Mspoc acyl fluorides are obtained in crystalline form,[1] in contrast to the undefined foams or amorphous products that are typically obtained with other protecting groups.

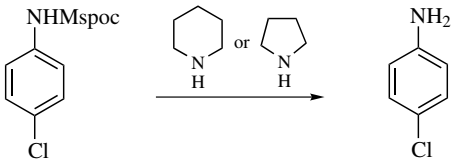


(5)

R=H, 82%
R=Bn, 81%

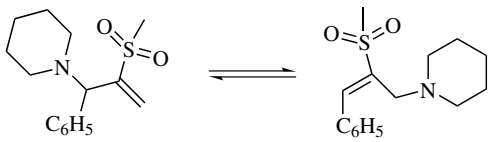


Deprotection of the Mspoc Group. The key deprotection method for this group involves the addition of a nucleophilic reagent to the α,β-unsaturated sulfone system with the consequent ejection of the carbamate anion. The major advantages of such a process over systems for which deprotection involves a classic β-elimination process [e.g., the 2-(methylsulfonyl)ethoxycarbonyl (Msc)[7] or 9-fluorenylmethyloxycarbonyl (Fmoc)[8] systems] are that (a) lower concentrations of piperidine or weaker bases can be used for deprotection, thus minimizing the base-catalyzed side reactions, and (b) application to the technique of rapid continuous synthesis is greatly improved. Piperidine or pyrrolidine can be used to deprotect the *N*-Mspoc amino compounds and the deprotection is found to be both more rapid and specific with the latter (eq 6).[1]



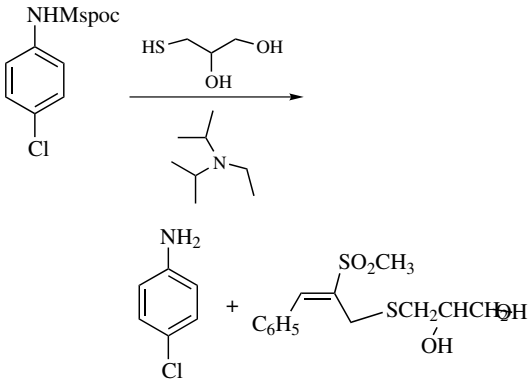
(6)

According to ^{1}H NMR analysis the initial Michael-like adduct, formed upon treatment of *N*-Mspoc amines with piperidine, exists in equilibrium with its regioisomer (eq 7).



(7)

The Mspoc group is also sensitive to the base-catalyzed mercaptan deprotection. For example, 3-mercapto-1,2-propanediol rapidly deprotects the Mspoc derivative of *p*-chloroaniline in the presence of diisopropylethylamine to give an equimolar mixture of the amine and the thio adduct (eq 8).[1]



(8)

Related Reagents. 2-(*tert*-Butylsulfonyl)-2-propenyl Chloroformate (Bspoc-Cl);[4] 1,1-Dioxobenzo[*b*]thiophene-2-ylmethyl Chloroformate (Bsmoc-Cl);[9] 9-Fluorenylmethyl Chloroformate (Fmoc-Cl);[8] 2-(Methylsulfonyl)ethyl Chloroformate (Msc-Cl).[7]

1. Carpino, L. A.; Mansour, E. M. E., *J. Org. Chem.* **1999**, *64*, 8399.
2. Doomes, E.; Overton, B. M., *J. Org. Chem.* **1987**, *52*, 1544.
3. Harris, M.; Bull, M. J., *Synth. Commun.* **1985**, *15*, 1225.
4. Carpino, L. A.; Philbin, M., *J. Org. Chem.* **1999**, *64*, 4315.
5. Carpino, L. A.; Sadat-Aalaee, D.; Chao H.-G.; DeSelms, R. H., *J. Am. Chem. Soc.* **1990**, *112*, 9651.
6. Carpino, L. A.; Mansour, E. M. E.; Sadat-Aalaee, D., *J. Org. Chem.* **1991**, *56*, 2611.
7. Tesser, G. I.; Balvert-Geers, I. C., *Int. J. Pept. Protein Res.* **1975**, *7*, 295.

8. Carpino, L. A., *Acc. Chem. Res.* **1987**, *20*, 401.
9. Carpino, L. A.; Philbin, M.; Ismail, M.; Truran, G. A.; Mansour, E. M. E.; Iguchi, S.; Ionescu, D.; El-Faham, A.; Riemer, C.; Warrass, R.; Weiss, M. S., *J. Am. Chem. Soc.* **1997**, *119*, 9915.

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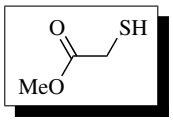
Methyl Thioglycolate

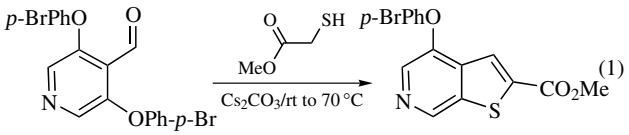


[2365-48-2] $C_3H_6O_2S$ (MW 106.14)
InChI = 1/C3H6O2S/c1-5-3(4)2-6/h6H,2H2,1H3
InChIKey = MKIJJIMOAABWGF-UHFFFAOYAP

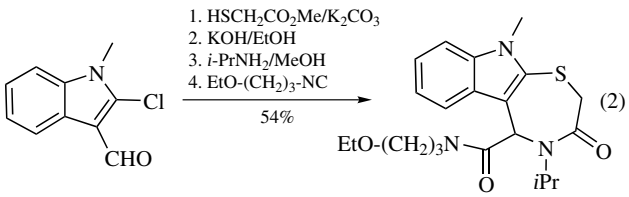
(building block for sulfur containing cyclic molecules, hydrogen atom donor, hydrogen atom abstractor)

Alternate Names: methyl 2-mercaptoacetate, thioglycolic acid methyl ester, mercaptoacetic acid methyl ester, MTG.
Physical Data: mp = −24 °C, bp = 42–43 °C (10 mm Hg), d = 1.187 (25 °C), pK_a = 7.91.[1]
Solubility: organic solvents (CH_2Cl_2, THF, C_6H_6, toluene), water (40 g/L (20 °C)).
Preparative Methods: commercially available.
Handling, Storage, and Precautions: harmful by inhalation and if swallowed, irritating to eyes, respiratory system, and skin. In case of contact with eyes, rinse immediately with plenty of water. Wear suitable protective clothing, gloves, and eye/face protection.

Heterocycle Synthesis. Methyl thioglycolate is a very interesting building block because the thiol function and the active methylene group are both potential nucleophiles and the ester group is an electrophile. Like other polyfunctional molecules, every functional group may react individually or in combination with the others. This ability has been widely used for the synthesis of sulfur containing heterocycles as exemplified in eqs 1[2] and 2.[3]

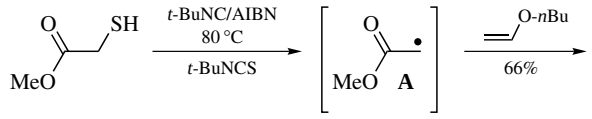


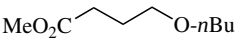
(1)



(2)

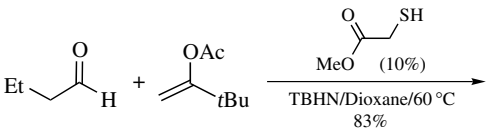
Radical Chain Reactions. By radical thiol desulfurization in presence of an isocyanide, MTG leads to the electrophilic radical **A** that can be trapped by a nucleophilic double bond (eq 3).[4]

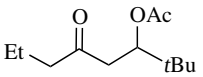




(3)

The presence of an electron withdrawing group increases the SH bond dissociation energy (BDE) relative to that of a simple alkanethiol.[5] For this reason, MTG is a good candidate to serve as a polarity reversal catalyst (PRC)[6] that promotes the overall hydrogen atom transfer from a substrate R–H to a carbon centered radical. This reactivity has been applied to the addition of aldehydes to alkenes (eq 4),[7] to the alkylation of electron-rich alkenes in the presence of silane (eq 5),[8] to the preparation of β-lactams via aminoacyl radical generation (eq 6),[9] and to hydroamination of double bonds (eq 7).[10]





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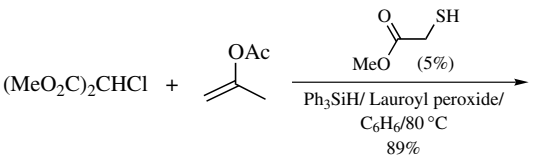
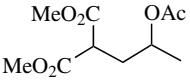
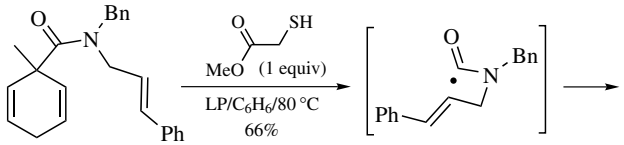
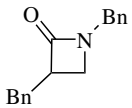




(5)





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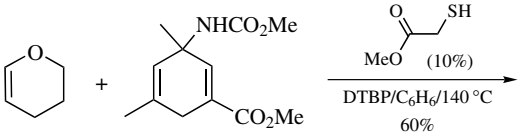
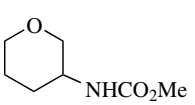
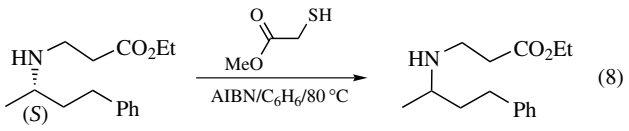




(7)

Methyl thioglycolate racemizes nonactivated aliphatic amines in the presence of AIBN at 80 °C. The process involves reversible

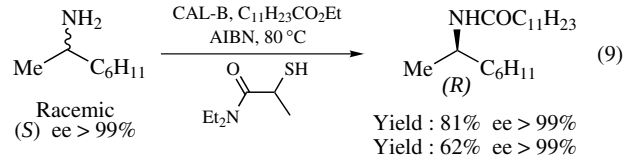
hydrogen atom-abstraction from the stereogenic center, in the α-position to the nitrogen, by the thiyl radical (eq 8). This reaction works with a stoichiometric or a catalytic amount of thiol.[5]



(8)

thiol	yield	*S* : *R*
1.2 equiv	80%	52 : 48
0.2 equiv	70%	59 : 41

The association of this thiol radical racemization reaction with a lipase-catalyzed enzymatic resolution enables the dynamic kinetic resolution of nonbenzylic amines with the CAL-B lipase. It leads to (*R*)-amides with high enantioselectivities. It can be applied either to the conversion of racemic mixtures or to the inversion of (*S*)-enantiomers. For optimum results, a slight modification of the thiol is required (eq 9).[11]



(9)

1. Hupe, D. J.; Jencks, W. P., *J Am. Chem. Soc.* **1977**, *99*, 451.
2. Zhu, G.-D.; Arendsen, D. L.; Gunawardana, I. W.; Boyd, S. A.; Stewart, A. O.; Fry, D. G.; Cool, B. L.; Kifle, L.; Schaefer, V.; Meuth, J.; Marsh, K. C.; Kempf-Grote, A. J.; Kilgannon, P.; Gallatin, W. M.; Okasinski, G. F., *J. Med. Chem.* **2001**, *44*, 3469.
3. Ilyn, A. P.; Loseva, M. V.; Vvedensky, V. Y.; Putsykina, E. B.; Tkachenko, S. E.; Kravchenko Dmitri, V.; Khvat, A. V.; Krasavin, M. Y.; Ivachtchenko, A. V., *J. Org. Chem.* **2007**, *71*, 2811.
4. Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Strazzari, S.; Zanardi G., *Angew. Chem., Int. Ed.* **2004**, *43*, 3598.
5. Gastaldi, S.; Vanthuyne, N.; Gil, G.; Siri, D.; Bertrand, M. P., *J. Org. Chem.* **2006**, *71*, 7288.
6. Roberts, B. P., *Chem. Soc. Rev.* **1999**, *28*, 25.
7. Dang, H.-S.; Roberts, B. P., *J. Chem. Soc., Perkin Trans.1* **1998**, 67.
8. Dang, H.-S.; Elsegood, M. R. J.; Kim, K.-M.; Roberts, B. P., *J. Chem. Soc., Perkin Trans. 1* **1999**, 2061.
9. Bella, A. F.; Jackson, L. V; Walton, J. C., *Org. Biomol. Chem.* **2004**, *2*, 421.
10. Kemper, J.; Studer, A., *Angew. Chem., Int. Ed.* **2005**, *44*, 4914.
11. Gastaldi, S.; Escoubet, S.; Vanthuyne, N.; Gil, G.; Bertrand, M. P., *Org. Lett.* **2007**, *9*, 837.

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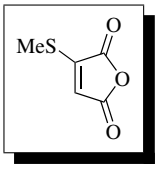
Université Paul Cézanne: Aix-Marseille III, Marseille, France

Methylthiomaleic Anhydride



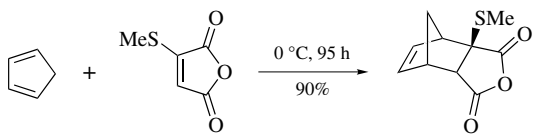
[64810-01-1] $C_5H_4O_3S$ (MW 144.16)
InChI = 1/C5H4O3S/c1-9-3-2-4(6)8-5(3)7/h2H,1H3
InChIKey = ZXSUNPYBGKFGSY-UHFFFAOYAN

(2π partner in [4 + 2] cycloaddition reactions;[1] synthon for methoxycarbonylketene or methyleneketene[5])

Alternate Name: 3-(methylthio)-2,5-furandione.
Physical Data: mp 36–37 °C (ether); bp 123–125 °C/0.5 mmHg.
Analysis of Reagent Purity: IR 1845, 1745, 1566 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.28, 2.56; ^{13}C NMR ($CDCl_3$) δ 162.4, 162.1, 155.5, 118.5, 15.2.
Preparative Method: prepared by the addition of methyl isothiocyanate to acetylenedicarboxylic acid (ethanol, 25 °C) to afford a 6:1 mixture of 2-(methylthio)fumaric and -maleic acids, which are dehydrated by dissolution in thionyl chloride for 1 h at 25 °C, then 7 h at 60 °C. Excess $SOCl_2$ is removed at 120 °C at aspirator pressure, followed by distillation of the residue to afford the crystalline anhydride in 68–77% yield.[1]

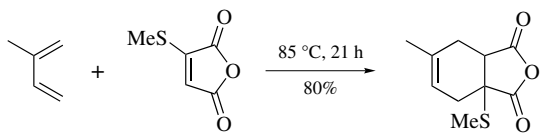
Reactivity. Methylthiomaleic anhydride (**1**) has been reported to react as a regioselective, *endo*-selective, electron-deficient 2π partner in [$_\pi 4_s + _\pi 2_s$] cycloaddition reactions.[1]

Cycloaddition Reactions.[1] Cycloadditions were carried out by mixing the neat dieneophile (**1**) with the appropriate diene at 0–80 °C in the presence of 2,6-di-*t*-butyl-4-methylphenol (BHT) or hydroquinone as a stabilizer. Exclusive *endo* selectivity was observed in the cycloaddition of cyclopentadiene with dienophile (**1**) to afford the bicyclo[2.2.1]heptene adduct (eq 1). Reaction of (**1**) with isoprene afforded the cyclohexene adduct as a single regioisomer (eq 2). Similarly, a single regioisomeric cycloadduct was observed with (**1**) and 1-vinyl-6-methoxy-3,4-dihydronaphthalene (eq 3). The thiomethyl group[2] was postulated to be responsible for the excellent regiocontrol observed in cycloadditions of (**1**), since comparable cycloadditions with methylmaleic anhydride exhibited poor regioselectivity.[3]



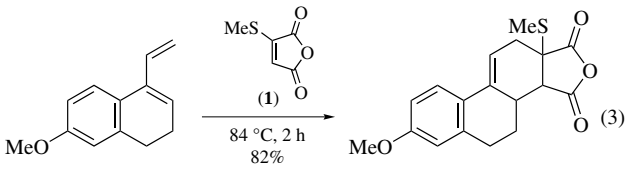
(1)

(1) *endo*



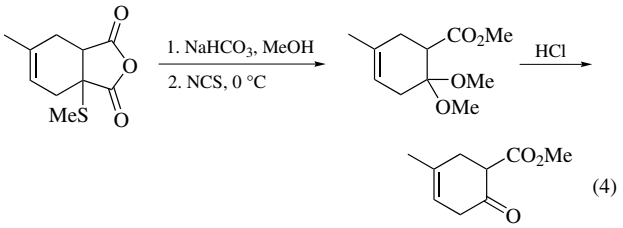
(2)

(**1**)



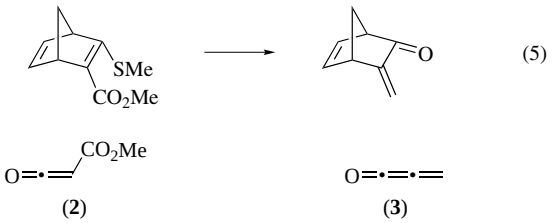
(3)

Oxidative decarboxylation[4] of cycloadducts of (**1**) affords access to β-keto ester functionality. Treatment of the isoprene–(**1**) cycloadduct with methanol followed by *N*-chlorosuccinimide afforded the corresponding dimethyl acetal, which could be hydrolyzed to afford the β-keto ester (eq 4).[1]



(4)

In bicyclic adducts (eq 1), thiol enol ethers are the direct products of oxidative decarboxylation; reduction of the ester and subsequent hydrolysis of the thiol enol ethers affords α-methylene ketones (eq 5).[5] Thus eqs (eq 4) and (eq 5) demonstrate the utility of (**1**) as a methoxycarbonylketene (**2**) or methyleneketene (**3**) synthon in [4 + 2] cycloaddition reactions.



(5)

1. Trost, B. M.; Lunn, G., *J. Am. Chem. Soc.* **1977**, *99*, 7079.
2. (a) Trost, B. M.; Bridges, A. J., *J. Am. Chem. Soc.* **1976**, *98*, 5017. (b) Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, R. J.; Ruffner, R. J.; Fabek, J. R., *J. Org. Chem.* **1976**, *41*, 3218. (c) Evans, D. A.; Bryan, C. A.; Sims, C. L., *J. Am. Chem. Soc.* **1972**, *94*, 2891.
3. Bachman, W. E.; Chemerda, J. M., *J. Am. Chem. Soc.* **1948**, *70*, 1468.
4. (a) Trost, B. M.; Tamaru, Y., *J. Am. Chem. Soc.* **1977**, *99*, 3101. (b) Trost, B. M.; Tamaru, Y., *Tetrahedron Lett.* **1975**, 3797. (c) Trost, B. M.; Tamaru, Y., *J. Am. Chem. Soc.* **1975**, *97*, 3528.
5. Trost, B. M., *Acc. Chem. Res.* **1978**, *11*, 453.

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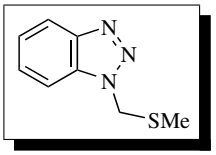
1-(Methylthiomethyl)benzotriazole



[183164-38-7] $C_8H_9N_3S$ (MW 179.25)

InChI = 1/C8H9N3S/c1-12-6-11-8-5-3-2-4-7(8)9-10-11/h2-5H, 6H2,1H3

InChIKey = XIBSFNFXWRFAMG-UHFFFAOYAZ

(bifunctional reagent for the coupling of alkyl halides, or carbonyl compounds, by a CO bridge; methylthiomethylene group donor in the synthesis of methylthiomethyl ketones from aromatic aldehydes; precursor in the synthesis of thioacylsilanes)

Physical Data: white plates, mp 60 °C.

Solubility: soluble in ether, THF, ethyl acetate, CH_2Cl_2, $CHCl_3$, and DMSO.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 5.72 (s, 2H), 7.43 (t, J = 8.2 Hz, 1H), 7.55 (t, J = 8.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.7, 50.7, 110.1, 120.0, 124.1, 127.4, 131.8, 146.4.

Preparative Methods: can be prepared by Pummerer reaction of benzotriazole, DMSO, and acetic anhydride.[1,2] The product is usually obtained as a mixture of benzotriazol-1-yl (strongly predominates, crystalline) and benzotriazol-2-yl (oil) isomers which, although separable by column chromatography, can be used together in all the reactions discussed below. The major impurity is 1-acetylbenzotriazole; the formation of which could be suppressed dramatically by a slight modification in the procedure,[3] which includes slow addition of a concentrated solution of benzotriazole in 2 equiv of DMSO to a warm (80–90 °C) mixture of acetic anhydride with 2 equiv DMSO. (Caution: overheating above 100 °C triggers a vigorous exothermic reaction.)

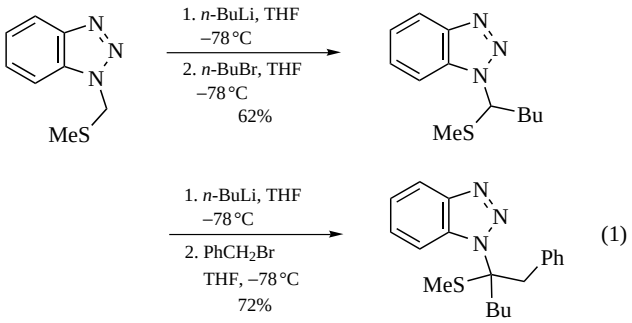
Purity: recommended isolation and purification steps include[3] (1) distilling excess Ac_2O and DMSO off the reaction mixture under reduced pressure; (2) dissolving the residue in ether or CH_2Cl_2 and washing off unreacted benzotriazole with an aq Na_2CO_3 solution; (3) removing the solvent and distillation of the residue under reduced pressure. This last distillation allows for removal of the residual 1-acetylbenzotriazole (bp 96–97 °C/1.5 mm Hg) from a mixture of (methyl thiomethyl)benzotriazole isomers (125–150 °C/1 mm Hg).

Handling, Storage, and Precaution: hygroscopic, shelf-stable, foul odor.

Introduction. All presently known organic synthesis applications of 1-(methylthiomethyl)benzotriazole are based on the high acidity of the methylene group protons (and, thus, ready formation of a carbanion) and on the possibility of selective cleavage of benzotriazolyl or methylthio groups under a variety of conditions.

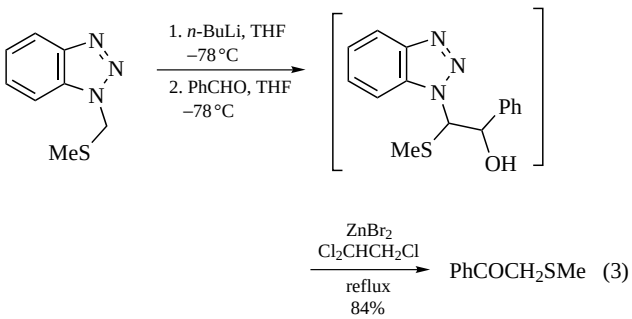
Synthesis of Ketones from Alkyl Halides or Carbonyl Compounds. 1-(Methylthiomethyl)benzotriazole serves as a useful alternative to the well-known carbonyl group synthetic

equivalents, such as 1,3-dithiane or tosylmethyl isocyanide, for the preparation of unsymmetrical ketones from alkyl and cycloalkyl halides (eqs 1 and 2).[2] Either *n*-BuLi or LDA is suitable as a base, and the reaction can be carried out in one-pot. While both the primary and secondary alkyl halides react smoothly in the first step, the second alkylation requires the use of a primary halide, probably due to increased steric hindrance at the reaction site. Subsequent acidic hydrolysis under mild conditions results in the cleavage of the thioaminal fragment converting it into a carbonyl group (eq 2).



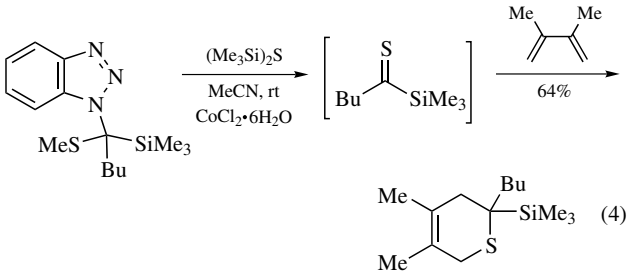
Other electrophiles, such as aromatic and aliphatic aldehydes, alicyclic ketones, or isocyanates, were also used successfully in the second step giving rise to unsymmetrical α-hydroxy ketones and α-keto amides after hydrolysis. Attempts to utilize an ester carbonyl group as an electrophile, however, failed; the reactions were low-yielding, and the expected products were accompanied by a number of byproducts.

Methylthiomethylene α-Insertion into Aldehydes and Ketones. Reactions of 1-(methylthiomethyl)benzotriazole with aldehydes and ketones following the lithiation–electrophilic substitution sequence discussed above, afford at the first step the α-hydroxyalkylated intermediates, the precursors to α-hydroxy ketones. Treatment of these aromatic aldehyde-derived intermediates with excess $ZnBr_2$ at elevated temperatures leads to intramolecular ring closure, with departure of the benzotriazolyl group, followed by 1,2-hydride shift, finally giving the formal products of insertion of the $MeSCH_2$ group into the C-H bond of the aldehyde carbonyl carbon group (eq 3).[1]



The analogous reaction with phenyl benzyl ketone gave both products of phenyl and benzyl group migration, with the latter predominating.

Synthesis of Acylsilanes. As masked analogs of α-oxo silanes, trimethylsilyl-substituted (methylthiomethyl)benzotriazoles, readily available from 1-(methylthiomethyl)benzotriazole via a lithiation-silylation procedure, undergo thionation with hexamethyldisilathiane (HMDST) in the presence of $CoCl_2$ hexahydrate.[4] Under these conditions, both benzotriazolyl and methylthio group are eliminated, and the resulting reactive thioacylsilanes could be trapped with dimethyl 1,3-butadiene (eq 4). The reaction yields are generally moderate and, though substrates with branched as well as non-branched α-substituents could be employed, the increased steric demand of an α-substituent leads to a noticeable decrease in yield.



Related Reagents. Tosylmethyl isocyanide; 1,3-Dithiane.

1. Katritzky, A. R.; Xie, L.; Serdyuk, L., *J. Org. Chem.* **1996**, *61*, 7564.
2. Katritzky, A. R.; Oniciu, D. C.; Ghiviriga, I.; Soti, F., *J. Org. Chem.* **1998**, *63*, 2110.
3. Pop, E.; Denisko, O. V.; Oniciu, D. C., unpublished results.
4. Degl'Innocenti, A.; Capperucci, A.; Oniciu, D. C.; Katritzky, A. R., *J. Org. Chem.* **2000**, *65*, 9206.

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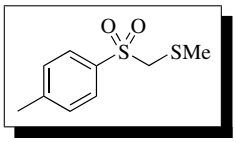
Methylthiomethyl *p*-Tolyl Sulfone[1]



[59662-68-9] $C_9H_{12}O_2S_2$ (MW 216.35)

InChI = 1/C9H12O2S2/c1-8-3-5-9(6-4-8)13(10,11)7-12-2/h3-6H,7H2,1-2H3

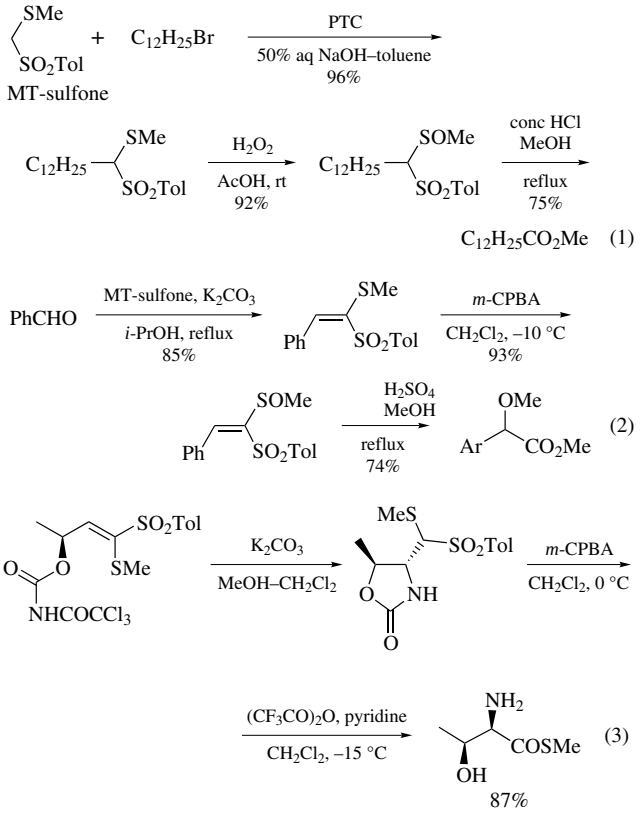
InChIKey = XAARLLNXZJTFPQ-UHFFFAOYAQ

(synthetic reagent for acyclic ketones, cyclic ketones, and conjugated unsaturated ketones)

Alternate Names: MT-sulfone; formaldehyde methyl *p*-tolyl dithioacetal *S,S*-dioxide; methyl *p*-toluenesulfonylmethyl sulfide; methylthio(*p*-toluenesulfonyl)methane.

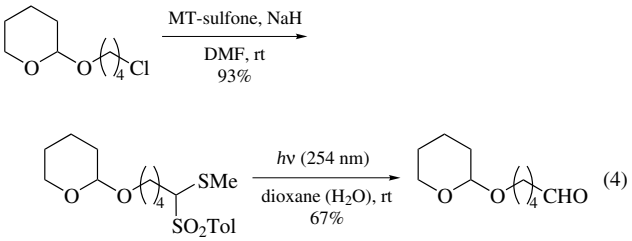
Physical Data: mp 82–83 °C; bp 164 °C/3 mmHg.
Solubility: sol DMF (87 g/100 mL), acetone (76 g/mL), $CHCl_3$ (57 g/mL), acetic acid (13 g/mL); slightly sol MeOH (5.8 g/mL), ethanol (3.3 g/mL), ethyl ether (3.0 g/mL), CCl_4 (2.2 g/mL); practically insol H_2O, hexane.
Form Supplied in: colorless crystals; commercially available.
Drying: over P_2O_5 in a desiccator.
Preparative Method: conveniently synthesized from dimethyl sulfoxide in a one-pot reaction, i.e. Pummerer reaction of DMSO with acetic anhydride followed by treatment with RS111.[2]
Handling, Storage, and Precautions: very stable under alkaline, acidic, and neutral conditions. Handle in a fume hood.

Synthesis of Esters and Aldehydes. Monoalkylation of methylthiomethyl *p*-tolyl sulfone (MT-sulfone) with an alkyl halide is achieved by the action of a phase-transfer catalyst (PTC) in toluene–50% aq NaOH.[3] sodium hydride[3] and butyllithium[4] also generate a carbanion of MT-sulfone. Arylmethyl derivatives of MT-sulfone are prepared by sodium borohydride reduction of the Knoevenagel condensation products with aromatic aldehydes.[5] The monoalkylated products are converted into the corresponding methyl esters (eq 1).[3,6] This functionalization can be utilized for synthesizing α-alkoxy carboxylic esters (eq 2)[3] and α-amino acids (eq 3).[7]

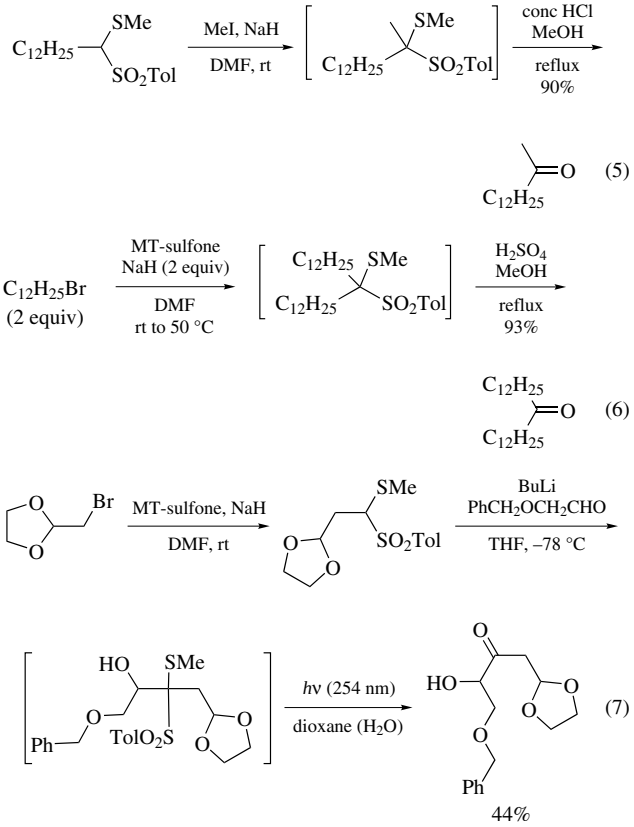


Irradiation (254 nm) of the monoalkylated product in dioxane–H_2O hydrolyzes the dithioacetal *S*,*S*-dioxide to produce an aldehyde. This method is suitably applied to the preparation of aldehydes which are susceptible to acidic conditions (eq 4).[8]

The carbanion of MT-sulfone is stable enough to add to α,β-unsaturated carbonyl compounds in a [1,4] fashion. The (methylthio)(*p*-tolylsulfonyl)methyl group introduced is easily converted into a (methylthio)carbonyl group or a formyl group.[4]

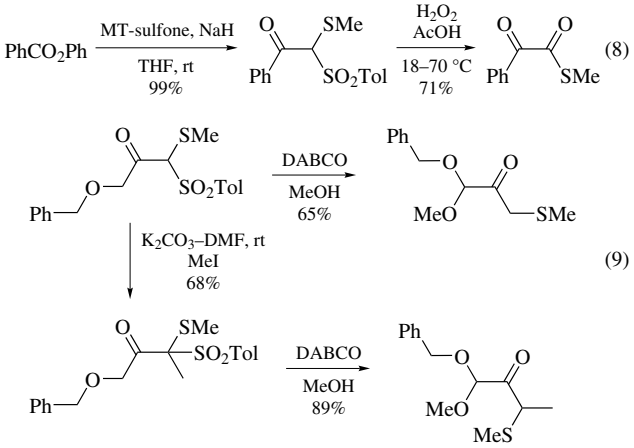


Ketone Synthesis. The monoalkylated MT-sulfone undergoes further alkylation by action of alkyl halide and NaH or *n*-BuLi to give a dialkylated product. Since the dialkylated product can be hydrolyzed easily, MT-sulfone has proven to be very useful for synthesizing ketones (eq 5).[5,8,9] Symmetrical ketones are prepared by direct dialkylation with NaH and alkyl halide in DMF and hydrolysis (eq 6).[8] Cyclic ketones are also synthesized from α,ω-dihaloalkanes.[3,10] An efficient synthesis of α-hydroxy ketones is also achieved by the addition of the monoalkyl derivative to an aldehyde to give an adduct and subsequent hydrolysis (eq 7).[11]

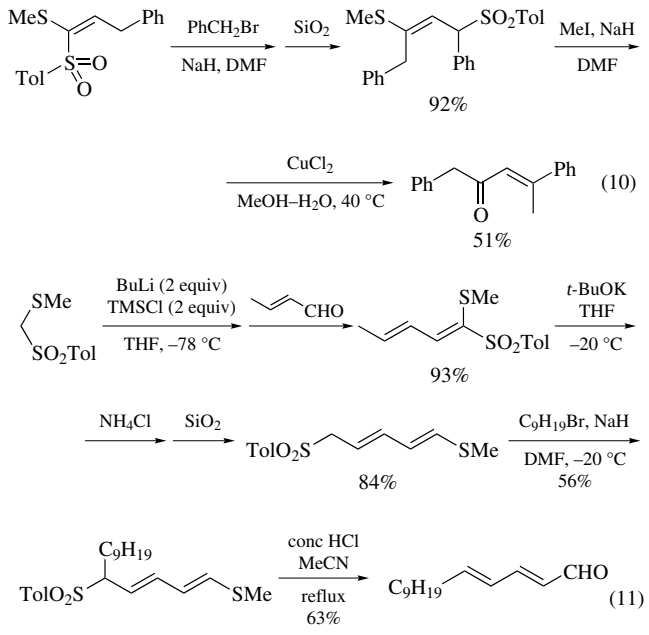


Acylation of MT-sulfone. MT-sulfone was acylated by treatment with an ester and excess NaH in THF.[3,12,13] The acylated MT-sulfone was oxidized with hydrogen peroxide in acetic acid, by slowly warming the reaction to give an *S*-methyl α-keto carbothioate (eq 8).[3]

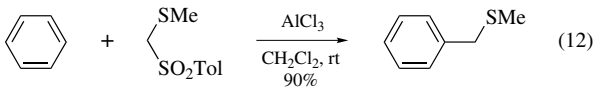
An alkoxyacetyl derivative of MT-sulfone exhibits intriguing behavior on treatment with a weak base to form an acetal of 3-methylthio-2-oxopropanal (eq 9).[14]



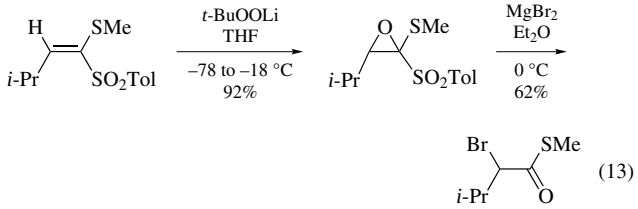
Synthesis of α,β-Unsaturated Ketones. Alkylidene derivatives of MT-sulfone are useful synthetic precursors for α,β-unsaturated ketones (eq 10).[15] This method can be extended to provide an efficient synthesis of α,β,γ,δ-unsaturated aldehydes and ketones (eq 11).[16,17]



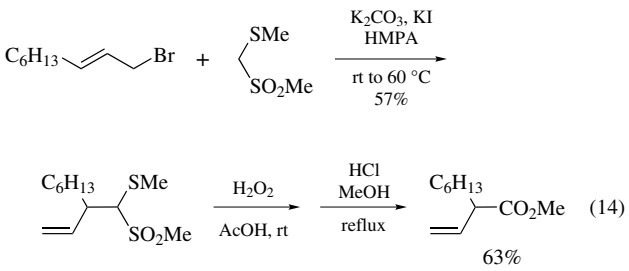
Electrophilic (Methylthio)methylation. Lewis acids such as aluminum chloride or ethylaluminum dichloride assist the heterolytic cleavage of the C–SO_2 bond of the dithioacetal *S,S*-dioxide to produce a MeS-stabilized carbocation, which reacts with allylsilanes[18] and benzene rings[19] (eq 12).



Reactivity of a 1-(Methylthio)-1-(*p*-tolylsulfonyl)-1-alkene. 1-(Methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes show extremely high reactivity towards carbon radicals to provide a synthetic route leading to new types of 1-methylthio-1-(*p*-tolylsulfonyl)-alkanes.[20,21] They also undergo nucleophilic epoxidation with lithium *tert*-butoxide to give an α,β-epoxy-α-methylthio sulfone, a precursor for an α-bromo thiol ester (eq 13).[22]



Methyl Methylthiomethyl Sulfone. Methyl methylthiomethyl sulfone is the *S*-methyl analog of MT-sulfone and it is conveniently synthesized by oxidation of methyl methylthiomethyl sulfoxide (FAMSO) with potassium permanganate or H_2O_2–NaOH.[23] It is useful for synthetic methods similar to those using MT-sulfone: synthesis of carboxylic esters,[24] ketones,[25] and α-alkoxy-α-arylacetates.[26] In the reaction of this reagent with allylic bromides, α-methylthio-γ,δ-unsaturated sulfones are obtained by stirring the bromide with potassium carbonate and potassium iodide in hexamethylphosphoric triamide (eq 14), which does not occur with MT-sulfone.[24]



Related Reagents. *N,N*-Diethylaminoacetonitrile; *N,N*-Dimethyldithiocarbamoylacetonitrile; (4a*R*)-(4aα,7α,8aβ)-Hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin; 2-Lithio-1,3-dithiane; Nitromethane; 1,1,3,3-Tetramethylbutyl Isocyanide; *p*-Tolylsulfonylmethyl Isocyanide; 2-(Trimethylsilyl)thiazole.

1. (a) Ogura, K., *Pure Appl. Chem.* **1987**, *59*, 1033. (b) Ogura, K. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1990; Vol. 6, p 307. (c) Ogura, K., *Rev. Heteroatom Chem.* **1991**, *5*, 85.
2. Ogura, K.; Yahata, N.; Watanabe, J.; Takahashi, K.; Iida, H., *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3543.
3. Ogura, K.; Yahata, N.; Hashizume, K.; Tsuyama, K.; Takahashi, K.; Iida, H., *Chem. Lett.* **1983**, 767.
4. Ogura, K.; Yahata, N.; Minoguchi, M.; Ohtsuki, K.; Takahashi, K.; Iida, H., *J. Org. Chem.* **1986**, *51*, 508.
5. Ogura, K.; Ohtsuki, K.; Takahashi, K.; Iida, H., *Chem. Lett.* **1986**, 1597.
6. Krohn, K.; Kohle, H.-J., *Liebigs Ann. Chem.* **1987**, 1037.
7. Hirama, M.; Hioki, H.; Ito, S., *Tetrahedron Lett.* **1988**, *29*, 3125.
8. Ogura, K.; Ohtsuki, K.; Nakamura, M.; Yahata, N.; Takahashi, K.; Iida, H., *Tetrahedron Lett.* **1985**, *26*, 2455.
9. Tsuzuki, K.; Yan, F.-S.; Otoguro, K.; Ohmura, S., *J. Antibiot.* **1991**, *44*, 774.
10. Carpino, L. A.; Lin, Y. Z., *J. Org. Chem.* **1990**, *55*, 247.
11. Ogura, K.; Tsuruda, T.; Takahashi, K.; Iida, H., *Tetrahedron Lett.* **1986**, *27*, 3665.
12. Ferdinand, G.; Schank, K., *Synthesis* **1976**, 406.

13. Ogura, K.; Yahata, N.; Takahashi, K.; Iida, H., *Tetrahedron Lett.* **1983**, *24*, 5761.
14. Ogura, K.; Uchida, T.; Tsuruda, T.; Takahashi, K., *Tetrahedron Lett.* **1987**, *28*, 5703.
15. Ogura, K.; Iihama, T.; Kiuchi, S.; Kajiki, T.; Koshikawa, O.; Takahashi, K.; Iida, H., *J. Org. Chem.* **1986**, *51*, 700.
16. Ogura, K.; Yahata, N.; Fujimori, T.; Fujita, M., *Tetrahedron Lett.* **1990**, *31*, 4621.
17. Yahata, N.; Fujita, M.; Ogura, K., *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3601.
18. (a) Simpkins, N. S., *Tetrahedron Lett.* **1988**, *29*, 6787. (b) Simpkins, N. S., *Tetrahedron* **1991**, *47*, 323.
19. Torisawa, Y.; Satoh, A.; Ikegami, S., *Tetrahedron Lett.* **1988**, *29*, 1729.
20. Ogura, K.; Yanagisawa, A.; Fujino, T.; Takahashi, K., *Tetrahedron Lett.* **1988**, *29*, 5387.
21. Ogura, K.; Sumitani, N.; Kayano, A.; Iguchi, H.; Fujita, M., *Chem. Lett.* **1992**, 1487.
22. Hewkin, C. T.; Jackson, R. F. W.; Clegg, W., *J. Chem. Soc., Perkin Trans. 1* **1991**, 3091.
23. Ogura, K.; Suzuki, M.; Tsuchihashi, G., *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1414.
24. Ogura, K.; Watanabe, J.; Iida, H., *Tetrahedron Lett.* **1981**, *22*, 4499.
25. Ogura, K.; Suzuki, M.; Watanabe, J.; Yamashita, M.; Iida, H.; Tsuchihashi, G., *Chem. Lett.* **1982**, 813.
26. Ogura, K.; Watanabe, J.; Takahashi, K.; Iida, H., *J. Org. Chem.* **1982**, *47*, 5404.

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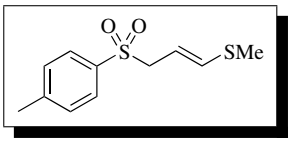
(*E*)-3-Methylthio-2-propenyl *p*-Tolyl Sulfone[1]



[92610-41-8] $C_{11}H_{14}O_2S_2$ (MW 242.39)
InChI = 1/C11H14O2S2/c1-10-4-6-11(7-5-10)15(12,13)9-3-8-14-2/h3-8H,9H2,1-2H3/b8-3+
InChIKey = VLLXZJAIJXTVGC-FPYGCLRLBP

(a synthetic reagent for preparation of α,β-unsaturated aldehydes and ketones)

Alternate Names: MTPTS; (*E*)-1-methylthio-3-(*p*-toluenesulfonyl)-1-propene.

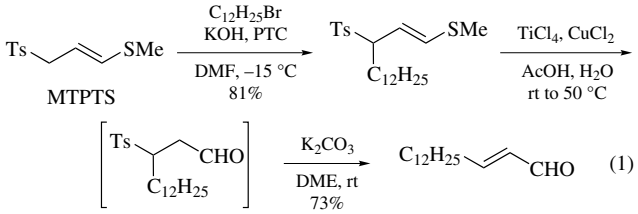
Physical Data: colorless crystals; mp 79–80 °C (from EtOH).

Solubility: sol DMF, $CHCl_3$; slightly sol MeOH, EtOH, diethyl ether, CCl_4; practically insol H_2O, hexane.

Preparative Methods: either by the reaction of sodium methanethiolate or dimethyl sulfide with 3-chloro-1-propenyl *p*-tolyl sulfone[2] or by α-selenylation of 3-(methylthio)propyl *p*-tolyl sulfone and subsequent oxidative dehydroselenylation.[3]

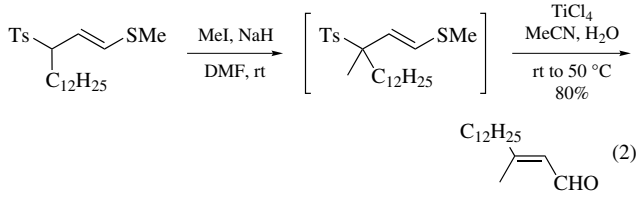
Handling, Storage, and Precautions: very stable at ambient temperature. Use in a fume hood.

Synthesis of α,β-Unsaturated Aldehydes. Monoalkylation of MTPTS can be achieved by treatment with an alkyl halide in the presence of potassium hydroxide–TOMAC (a phase-transfer catalyst) or sodium hydride in DMF.[4] The reaction of the monoalkylation product with titanium(IV) chloride and copper(II) chloride in acetic acid–water followed by treatment with potassium carbonate in DME affords α,β-unsaturated aldehydes (eq 1).



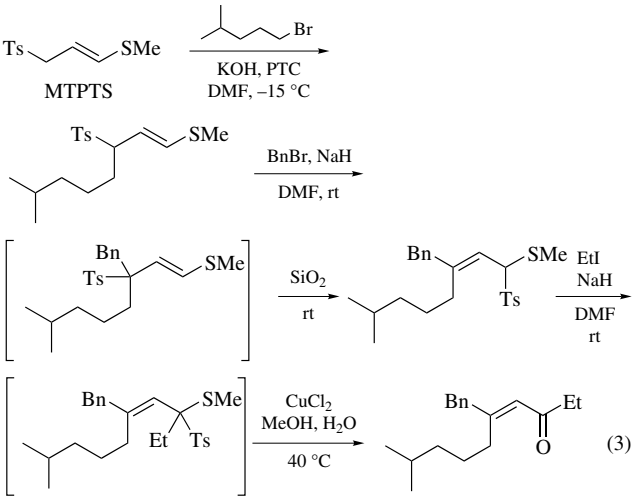
(1)

The second alkylation of MTPTS also occurs regiospecifically at the carbon α to the sulfonyl group. Since the dialkylated product is sensitive to silica gel, the reaction mixture is subjected without purification to hydrolysis with $TiCl_4$ and $CuCl_2$ in acetic acid–water to yield directly the corresponding β,β-disubstituted α,β-unsaturated aldehyde (eq 2).



(2)

Synthesis of α,β-Unsaturated Ketones. The dialkylated MTPTS undergoes a facile 1,3-rearrangement of its sulfonyl group on silica gel and a thermodynamically stable 2-alkenal dithioacetal *S,S*-dioxide is produced.[5] Since it has an active proton, the rearrangement product can be further alkylated. Subsequent hydrolysis of the alkylated product with $CuCl_2$ in methanol–water produces α,β-unsaturated ketones (eq 3). The synthetic method using MTPTS is characterized by its wide applicability to make various α,β-unsaturated ketones, three substituents of which are optionally and regiospecifically selected.



(3)

63% (*E*):(*Z*) = 2:1

Related Reagents. 1,3-Dibutoxy-1-lithio-1-propene; 1-Methoxyallenyllithium; 3-(Phenylsulfonyl)propanal Ethylene Acetal.

1. (a) Ogura, K., *Pure Appl. Chem.* **1987**, *59*, 1033. (b) Ogura, K. In *Studies in Natural Product Chemistry*; Atta-ur-Raman, Ed.; Elsevier: Amsterdam, 1990, Vol. 6, p 307.
2. Ogura, K.; Iihama, T.; Takahashi, K.; Iida, H., *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3347.
3. Hirata, T.; Sasada, Y.; Ohtani, T.; Asada, T.; Kinoshita, G.; Senda, H.; Inomata, K., *Bull. Chem. Soc. Jpn.* **1992**, *65*, 75.
4. Ogura, K.; Iihama, T.; Takahashi, K.; Iida, H., *Tetrahedron Lett.* **1984**, *25*, 2671.
5. Ogura, K.; Iihama, T.; Kiuchi, S.; Kajiki, T.; Koshikawa, O.; Takahashi, K.; Iida, H., *J. Org. Chem.* **1986**, *51*, 700.

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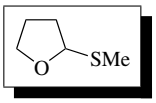
2-(Methylthio)tetrahydrofuran



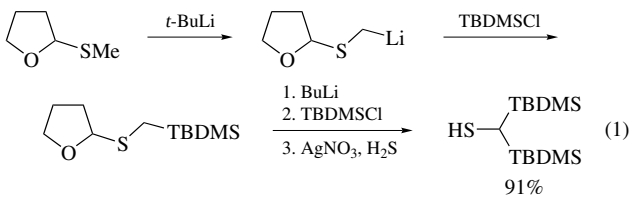
[98194-87-7] $C_5H_{10}OS$ (MW 118.22)
InChI = 1/C5H10OS/c1-7-5-3-2-4-6-5/h5H,2-4H2,1H3
InChIKey = KLRFYMVEGHDRFU-UHFFFAOYAN

(methanethiol carbanion, $HSCH_2^-$, equivalent[1])

Physical Data: bp 66–67 °C/21 mmHg; n_D^{20} 1.4868.[2]

Preparative Methods: conveniently prepared in two steps in 46% yield from THF by light-initiated α-chlorination with sulfuryl chloride at −30 °C followed by reaction with methanethiol/triethylamine at −78 °C.[2] Deprotonation with butyllithium gives 2-tetrahydrofuranyl(thiomethyl)lithium *[98194-88-8]*.[1]

Thiol and Disulfide Synthesis. Reaction of 2-tetrahydrofuranyl(thiomethyl)lithium with *tert*-butyldimethylchlorosilane, followed by *n*-BuLi and a second equivalent of *t*-butyldimethylchlorosilane followed by hydrolysis of the adduct with silver(I) nitrate or mercury(II) chloride followed by hydrogen sulfide or hydrogen chloride gives bis(*t*-butyldimethylsilyl)-methanethiol (t-$BuMe_2Si)_2CHSH$; 91%) (eq 1).[1]



(1)

Related Reagents. 2-(Methylthio)tetrahydropyran.

1. Block, E.; Aslam, M., *J. Am. Chem. Soc.* **1985**, *107*, 6729.
2. Brown, H. C.; Midland, M. M., *J. Am. Chem. Soc.* **1971**, *93*, 3291.

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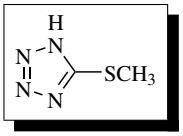
5-Methylthio-1*H*-tetrazole



[29515-99-9] $C_2H_4N_4S$ (MW 116.15)
InChI = 1/C2H4N4S/c1-7-2-3-5-6-4-2/h1H3,(H,3,4,5,6)/f/h3H
InChIKey = ZBXNFTFKKOSPLD-TULZNQERCG

(coupling agent for the synthesis of oligonucleotides using the phosphoramidite method)

Physical Data: mp 149–151 °C.

Solubility: partially soluble in water; soluble in DMF and CH_3CN.

Form Supplied in: crystalline solid.

Preparative Methods: this reagent can be readily prepared from methyl thiocyanate and sodium azide in the presence of ammonium chloride in anhydrous DMF.[1,2] Alternatively, it can be prepared by the reaction of methyl thiocyanate and sodium azide in water with zinc bromide as the catalyst.[3]

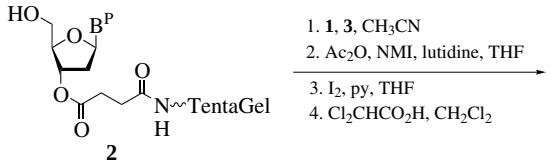
Purity: recrystallize from water or dioxane.

Handling, Storage, and Precaution: this reagent should be handled with precaution. It may be irritating to the eyes, the respiratory system, and harmful to the skin. Avoid contact with strong heat and metal salts since tetrazoles may be explosive. It should be stored in the dark in a desiccator.

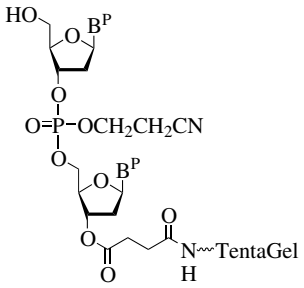
Activation of Phosphoramidites in Nucleotide Synthesis. Similar to 5-(4-nitrophenyl)-1*H*-tetrazole, 5-methylthio-1*H*-tetrazole (**1**) is a more efficient activator of phosphoramidites than 1*H*-tetrazole in the synthesis of oligonucleotides.[4] This reagent gives 2% higher average yield per coupling cycle than 1*H*-tetrazole as well as higher purity oligonucleotide product. Compared to 5-(4-nitrophenyl)-1*H*-tetrazole, which has poor solubility in acetonitrile (<0.12 M),[5] 5-methylthio-1*H*-tetrazole has a greater solubility (>2.0 M in acetonitrile) and is more suitable for application in large-scale synthesis of oligonucleotides on high loading support. Thus, the TentaGel-supported nucleoside (**2**) (loading 137–193 μmoles per gram) is readily coupled to the phosphoramidite **3** (eq 1) with the total synthesis time for four complete cycles (coupling, capping, oxidation, and detritylation) being only 45 min. The average stepwise yield for the synthesis of an 18mer oligonucleotide 5′TCACAGTCTGAT CTCGAC3′has been estimated to be 96.6% on a 1-mmole scale synthesis.

The use of 5-methylthio-1*H*-tetrazole as the coupling agent also allows the primary hydroxyl group in unprotected carbohydrates and nucleosides to be selectively phosphitylated (eq 2).[6] When the same reactions are performed with 1*H*-tetrazole as the activator, much worse selectivity is observed, resulting in diminished yields.

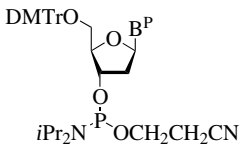
Other Applications. 5-Methylthio-1*H*-tetrazole has also been used for the synthesis of phosphoramidite and phosphite triester containing platinum complexes (eqs 3 and 4).[7]



2

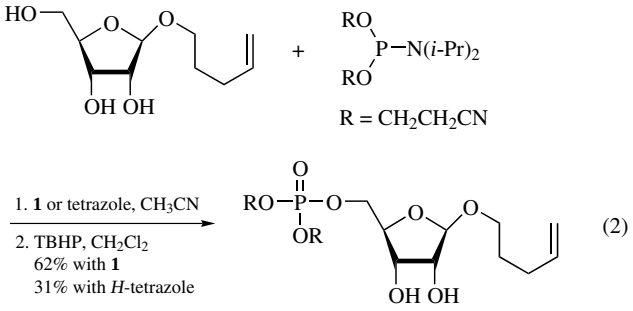


(1)

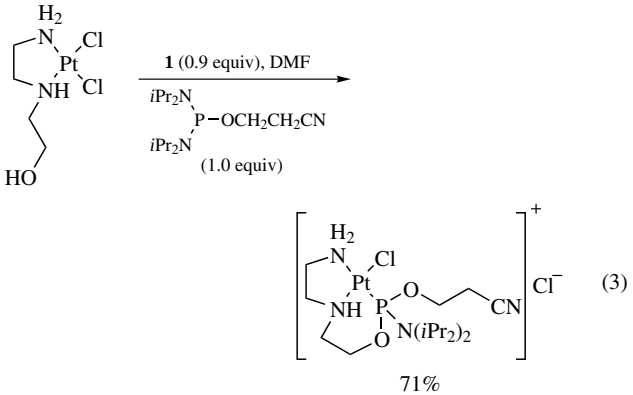


3

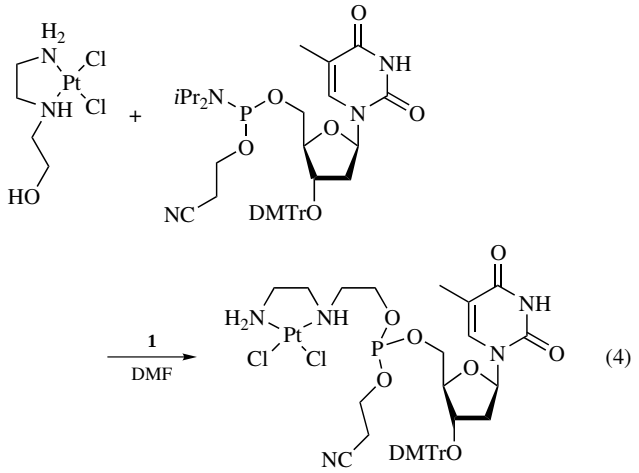
B^{p} (a general protected base) =A^{bz}, G^{ibu}, C^{bz}, and T



(2)



(3)



(4)

Related Reagents. 5-(4-Nitrophenyl)-1*H*-tetrazole.

1. Finnegan, W. G.; Henry, R. A.; Lofquist, R., *J. Am. Chem. Soc.* **1958**, *80*, 3908.
2. Lieber, E.; Enkoji, T., *J. Am. Chem. Soc.* **1961**, *26*, 4472.
3. Demko, Z. P.; Sharpless, K. B., *J. Org. Chem.* **2001**, *66*, 7945.
4. Wright, P.; Lloyd, D.; Rapp, W.; Andrus, A., *Tetrahedron Lett.* **1993**, *34*, 3373.
5. Froehler, B. C.; Matteucci, M. D., *Tetrahedron Lett.* **1983**, *24*, 3171.
6. Graham, S. M.; Pope, S. C., *Org. Lett.* **1999**, *1*, 733.
7. Ren, S.; Cai, L.; Segal, B. M., *J. Chem. Soc., Dalton Trans.: Inorg. Chem.* **1999**, 1413.

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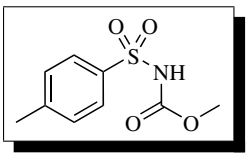
Methyl *N*-(*p*-Toluenesulfonyl)carbamate



[14437-03-7] $C_9H_{11}NO_4S$ (MW 229.25)

InChI = 1/C9H11NO4S/c1-7-3-5-8(6-4-7)15(12,13)10-9(11)14-2/h3-6H,1-2H3,(H,10,11)/f/h10H

InChIKey = KNVDHKOSDVFZTO-KZFATGLACU

(reagent used to introduce a protected amino group)

Physical Data:[1] mp 111–113 °C (lit. 115 °C[2a], 108–111 °C[2b]), after recrystallization from CCl_4.

Solubility: soluble in DMSO, MeOH, THF, AcOEt, $CHCl_3$, CH_2Cl_2; insoluble in H_2O.

Analysis of Reagent Purity: NMR data[3] for the reagent: 1H-NMR ($CDCl_3$): δ2.45 (3H, s), 3.71 (s, 3H), 7.35 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H), 7.40–7.65 (br s, 1H); 13C-NMR (DMSO-d_6): δ 21.4, 53.2, 127.8, 129.9, 136.7, 144.6, 152.0.

Preparative Methods: prepared from commercially available *p*-toluenesulfonamide.

Method A:[3] Methyl chloroformate (4.43 mL, 0.060 mol) was slowly added to a solution of *p*-toluenesulfonamide (6.48 g, 0.040 mol) and Et_3N (10.12 g, 0.100 mol) in anhydrous CH_3CN (40 mL). The resulting solution was stirred at room temperature for 6 h and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc and aq $NaHCO_3$ was added. The water layer was separated and acidified with a mixture of ice and conc HCl to give an oily precipitate that slowly crystallized upon standing. The crystals were collected by filtration, washed with water, and dried to give the reagent (4.09 g, 45% yield, 107–108 °C).

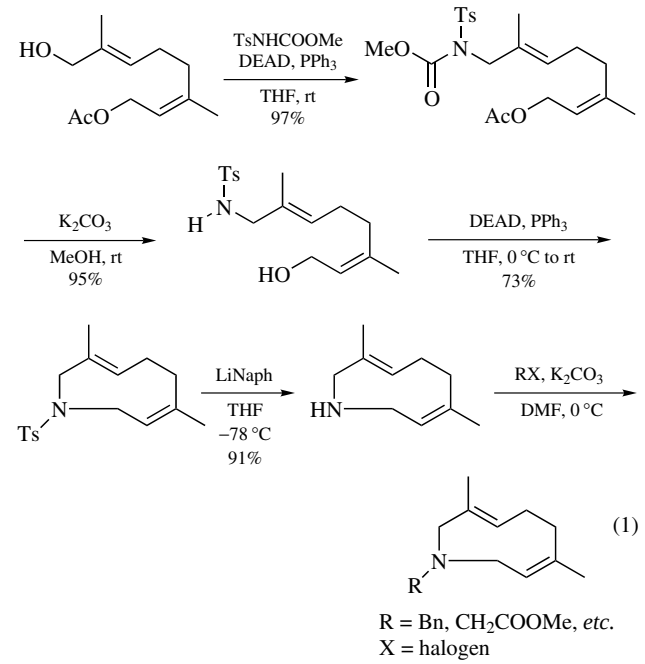
Method B:[4] To a suspension of *p*-toluenesulfonamide (24.3 g, 0.14 mol) in MeOH (30 ml), NaOMe (30 wt. % in MeOH, 37.9 g) was added, and the mixture was stirred at room temperature. *p*-Toluenesulfonamide was dissolved exothermically to give the sodium salt. After the addition of dimethylcarbonate (15.2 g, 0.17 mol), the mixture was refluxed for 18 h. The volatiles and excess dimethylcarbonate were evaporated. The residue was dissolved in water and the solvent was adjusted to pH 2 with conc HCl (23 g). The resulting precipitate was filtrated to give the reagent (30.9 g, 95% yield).

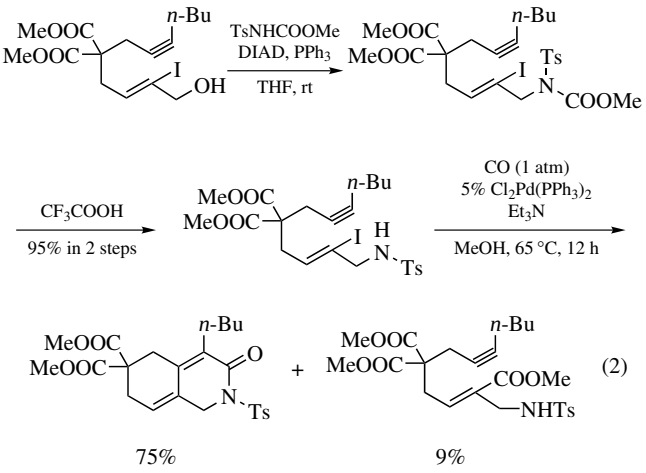
Method C:[5] To a solution of *N*-chloro-*p*-toluenesulfonamidate potassium (1.9 g, 7.7 mmol) in CH_3CN (10 ml), $Pd(PhCN)_2Cl_2$ (120 mg) and MeOH (0.27 g, 8.5 mmol) were added and stirred at 25 °C for 3 h under CO (g) (initial pressure 4.2 MPa). After the CO (g) consumption has stopped, the volatiles were evaporated. The solid residue was recrystallized to give the reagent (1.42 g, 80% yield).

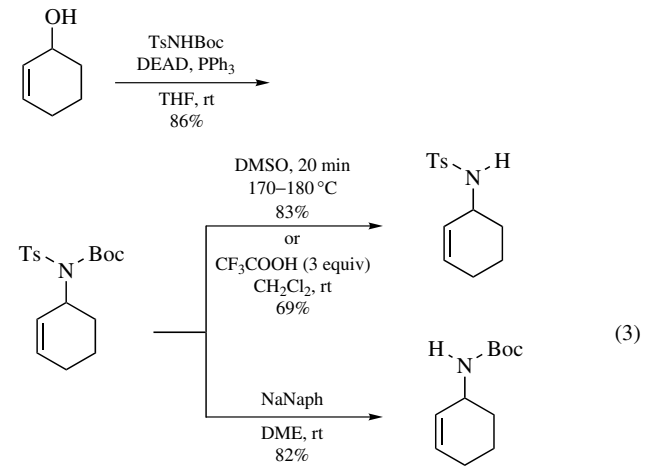
Introduction of Protected Amino Group. Methyl *N*-(*p*-toluenesulfonyl)carbamate serves as an equivalent of ammonia to which diverse alkyl groups can be introduced stepwise, thereby providing methodology for the synthesis of various primary, secondary, and tertiary amines. The reagent can be successfully applied to the synthesis of a nine-membered tertiary amine ring (eq 1).[6] Introduction of the reagent to the allylic alcohol is conducted under standard Mitsunobu conditions[7,8] to give the corresponding carbamates in excellent yield. The methoxycarbonyl group of the carbamate can be removed under mild basic conditions (K_2CO_3, MeOH, room temperature) to afford the corresponding sulfonamides, which are alkylated with internal alcohols by the Mitsunobu reaction and formed a cyclic compound with a protected secondary amine. After removal of the tosyl protection, the third alkyl group is introduced to the amine by treatment with alkyl halide, giving an *N*-alkylated cyclic amine.

This reagent is employed effectively for the synthesis of fused-ring lactams. In this case, the methoxycarbonyl group is removed under acidic conditions such as CF_3COOH (eq 2).[9] Following treatment with a Pd-catalyst under a CO atmosphere, the tosylated 2-iodoallylamine cyclizes to a triple bond intramolecularly by carbopalladation of alkynes followed by carbonylative amidation.

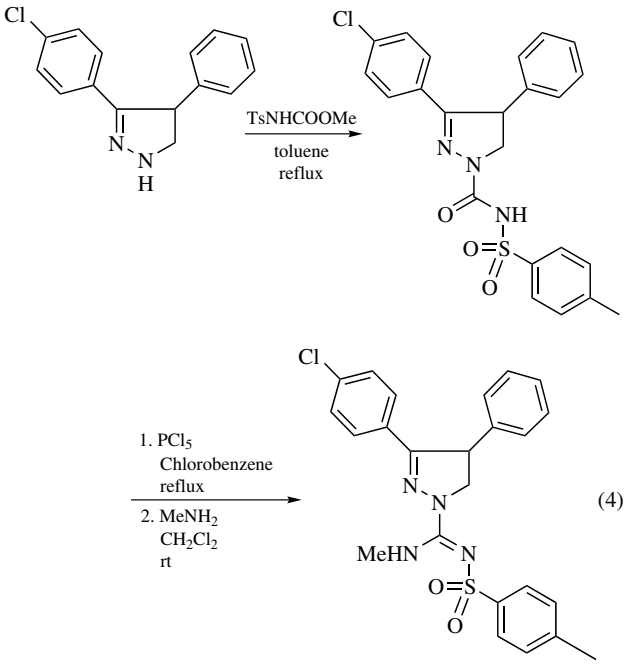
The related *N*-Boc compound, *tert*-butyl *N*-(*p*-toluenesulfonyl) carbamate, is also used for the synthesis of protected secondary amines in a similar manner. In this case, both of the amine protecting groups can be selectively removed (eq 3).[8] The tosyl group is deprotected selectively by sodium naphthalenide[10] to give the *N*-Boc amino compound. Alternatively, selective deprotection of the Boc group is carried out by thermolysis in DMSO or treatment with CF_3COOH to provide the *N*–Ts amino compound.





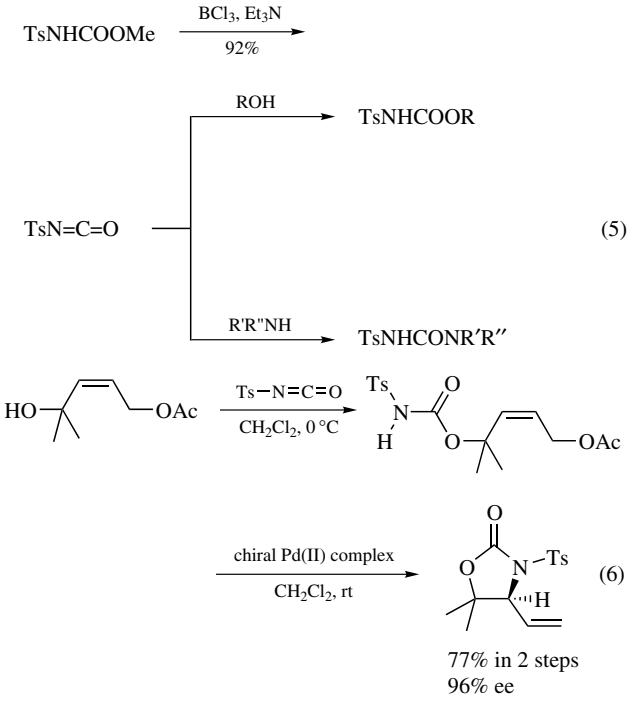


Reaction with Amino Derivatives. Methyl *N*-(*p*-toluenesulfonyl)carbamate serves as an electrophilic partner in the substitution reaction with amines and afforded a good yield of sulfonylurea derivatives.[11] The sulfonylurea derivatives so obtained were converted into carboxamidine derivatives in moderate yields via the imidoyl chloride intermediates, which are prepared by chlorination using phosphorus pentachloride in chlorobenzene and showed high reactivity with a broad range of amines (eq 4).



(4)

Preparation of *p*-Tosyl Isocyanates. Aryl sulfonyl isocyanate[5] is generally prepared by the reaction of phosgene or oxalyl chloride with sulfonamide[12,13] and also trimethylsilyl isocyanate with arylsulfonyl chloride in the presence of titanium tetrachloride.[14] These methods use toxic materials such as phosgene and other chlorine-containing compounds. Butler and Alper[15] have synthesized aryl sulfonyl isocyanate from methyl *N*-(*p*-toluenesulfonyl)carbamate on treatment with boron trichloride in the presence of triethylamine (eq 5). The reaction can be performed under mild conditions and both treatment and work-up are easy and simple. The isocyanates are isolated in excellent yields after evaporation under reduced pressure of the solvent and the resulting trialkyl borate. *p*-Toluenesulfonyl isocyanates can be used to prepare other *p*-toluenesulfonyl carbamate derivatives by reaction with primary, secondary, or tertiary alcohols.[16] The reaction is applied to the synthesis of a 2-oxazolidinone derivative (eq 6). The reaction of tertiary allylic alcohols with *p*-toluenesulfonyl isocyanate afforded the corresponding allylic *N*-(*p*-toluenesulfonyl)carbamates, which are used for the enantioselective synthesis of vinyl-substituted 2-oxazolodines by employing chiral Pd (II) complexes. By reaction with various amines,[17] the *p*-toluenesulfonyl isocyanate produces a *p*-toluenesulfonyl urea derivative (eq 5). This affords an alternative to the above-mentioned direct reaction of methyl *N*-(*p*-toluenesulfonyl)carbamate and amines.



(5)

(6)

1. Ulrich, H.; Tucker, B.; Stuber, F. A.; Sayigh, A. A. R., *J. Org. Chem.* **1969**, *34*, 2250.
2. (a) Boehringer, C. F.; Soehne, G. M. B. H., *Neth. Appl.* **1966**, NL 6603399; Chem. Abstr. **1967**, *66*, 55245. (b) Borsus, J. M.; L'abbe, G.; Smets, G., *Tetrahedron* **1975**, *31*, 1537.
3. Lange, J. H. M.; Coolen, H. K. A. C.; van Stuivenberg, H. H.; Dijksman, J. A. R.; Herremans, A. H. J.; Ronken, E.; Keizer, H. G.; Tipker, K.; McCreary, A. C.; Veerman, W.; Wals, H. C.; Stork, B.; Verveer, P. C.; den Hartog, A. P.; de Jong, N. M. J.; Adolfs, T. J. P.; Hoogendoorn, J.; Kruse, C. G., *J. Med. Chem.* **2004**, *47*, 627.
4. Takahashi, Y.; Iwasaki, H.; Noguchi, K., *Jpn. Kokai Tokkyo Koho* **1994**, JP 06298723.
5. Besenyei, G.; Nemeth, S.; Simandi, L.; Belak, M.; Dukai, J.; Nagy, L.; Tomordi, E.; Soptei, C.; Dioszegi, E. E., *Ger. Offen.* **1989**, DE 3919747.
6. (a) Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K., *Org. Lett.* **2006**, *8*, 9. (b) Tomooka, K.; Suzuki, M.; Shimada, A.; Yanazuru, S., *Jpn. Kokai Tokkyo Koho* **2003**, JP 2003261538. (c) Araújo, M. E. M.; Campelo, M.; Iley, J.; Norberto, F., *J. Chem. Soc., Perkin Trans. 2* **2001**, 494.
7. For reviews, see: (a) Mitsunobu, O., *Synthesis* **1981**, *1*. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
8. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.
9. Coperet, C.; Sugihara, T.; Negishi, E., *Tetrahedron Lett.* **1995**, *36*, 1771.
10. (a) Ji, S.; Goltler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P., *J. Am. Chem. Soc.* **1967**, *30*, 245. (b) Stork, G.; Mah, R., *Hetrocycles* **1989**, *28*, 723.
11. (a) Lange, J. H. M.; Coolen, H. K. A. C.; Van Stuivenberg, H. H.; Dijksman, J. A. R.; Herremans, A. H. J.; Ronken, E.; Keizer, H. G.; Tipker, K.; McCreary, A. C.; Veerman, W.; Wals, H. C.; Stork, B.; Verveer, P. C.; den Hartog, A. P.; de Jong, N. M. J.; Adolfs, T. J. P.; Hoogendoorn, J.; Kruse, C. G., *J. Med. Chem.* **2004**, *47*, 627. (b) Cassady, D. R.; Ainsworth, C.; Easton, N. R.; Livezey, M.; Sigal, M. V., Jr; Van Heyningen, E., *J. Org. Chem.* **1958**, *23*, 923. (c) Marshall, F. J.; Sigal, M. V., Jr., *J. Org. Chem.* **1958**, *23*, 927.
12. (a) Anilin, B.; Fabrik, S., **1953**, GB 692360. (b) Ulrich, H.; Tucker, B.; Sayigh, A. A. R., *J. Org. Chem.* **1969**, *34*, 3200. (c) Tsukajima, K.; Tezaki, K.; Kinpei, K., *Jpn. Kokai Tokkyo Koho*, **1999**, JP 11152264.

13. Franz, J. E.; Osuch, C., *J. Org. Chem.* **1964**, *29*, 2592.
14. Karl, R., *Ger. Offen.* **1984**, DE 3235045.
15. Butler, D. C. D.; Alper, H., *Can. Chem. Commun.* **1998**, *23*, 2575.
16. Overman, L. E.; Remarchuk, T. P., *J. Am. Chem. Soc.* **2002**, *124*, 12.
17. Ulrich, H., *Chem. Rev.* **1965**, *65*, 369, and the references cited therein.

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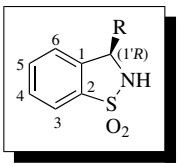
α-Methyltoluene-2,α-sultam[1]

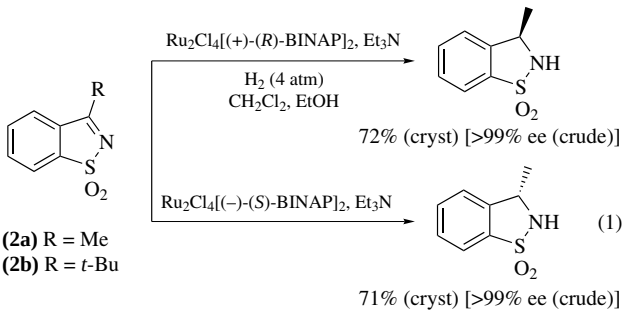


(1′*S*)-(**1a**; R = Me)
[130973-57-8] $C_8H_9NO_2S$ (MW 183.25)
InChI = 1/C8H9NO2S/c1-6-7-4-2-3-5-8(7)12(10,11)9-6/h2-6, 9H,1H3/t6-/m0/s1
InChIKey = WZOKMILQIPCVQJ-LURJTMIEBN
(1′*R*)-(**1a**)
[130973-53-4] $C_{11}H_{15}NO_2S$ (MW 225.34)
InChI = 1/C8H9NO2S/c1-6-7-4-2-3-5-8(7)12(10,11)9-6/h2-6, 9H,1H3/t6-/m1/s1
InChIKey = WZOKMILQIPCVQJ-ZCFIWIBFBP
(1′*S*)-(**1b**; R = *t*-Bu)
[137694-01-0]
InChI = 1/C11H15NO2S/c1-11(2,3)10-8-6-4-5-7-9(8)15(13,14)12-10/h4-7,10,12H,1-3H3/t10-/m1/s1
InChIKey = OHTMJLXKKSHARP-SNVBAGLBBB
(1′*R*)-(**1b**)
[137694-00-9]
InChI = 1/C11H15NO2S/c1-11(2,3)10-8-6-4-5-7-9(8)15(13,14)12-10/h4-7,10,12H,1-3H3/t10-/m0/s1
InChIKey = OHTMJLXKKSHARP-JTQLQIEIBN

(chiral auxiliary: *N*-enoyl derivatives undergo highly stereoselective Diels–Alder reactions with cyclopentadiene[2] and 1,3-dipolar cycloadditions with nitrile oxides;[3] enolates of *N*-acyl derivatives participate in highly stereoselective alkylations, acylations, and aldolizations[4])

Physical Data: (**1a**) mp 92 °C. (1′*S*)-(**1a**) $[\alpha]_D^{20}$ −30.0° (*c* 1.21, $CHCl_3$). (1′*R*)-(**1a**) $[\alpha]_D^{20}$ +31.0° (*c* 0.6, EtOH). (**1b**) mp 129–130 °C. (1′*S*)-(**1b**) $[\alpha]_D^{20}$ −53.9° (*c* 1.00, $CHCl_3$). (**1b**) has been incorrectly assigned.[3]

Preparative Methods: both enantiomers of the α-methyl sultam may be prepared on a multigram scale in optically pure form by asymmetric hydrogenation of imine (**2a**) followed by simple crystallization (eq 1).[5] The (*R*)-enantiomer of the α-*t*-butyl sultam may also be prepared in enantiomerically pure form by asymmetric reduction of imine (**2b**) followed by fractional crystallization.[3] However, multigram quantities of either enantiomer of the α-*t*-butyl sultam may be prepared by derivatization of the racemic auxiliary (obtained in 98% yield from reaction of (**2b**) with sodium borohydride in MeOH) with 10-camphorsulfonyl chloride1, separation of the resulting diastereomers by fractional crystallization, and acidolysis.[3] Prochiral imines (**2a**) and (**2b**) are readily prepared from inexpensive Saccharine by treatment with methyllithium (73%) and *tert*-butyllithium (66%), respectively.



Handling, Storage, and Precautions: these auxiliaries are white crystalline solids which are stable indefinitely at ambient temperature in sealed containers.

Introduction. The toluene-2,α-sultams are recently introduced relatives of the well established 10,2-camphorsultam chiral auxiliary and have been designed to provide similar high levels of face discrimination in reactions of pendent prochiral functionality. Features that distinguish them include high crystallinity and facile NMR and HPLC analysis of derivatives, favorable acylation and aldolization characteristics of derived *N*-acyl enolates, and improved cleavage characteristics.

Preparation of Derivatives. *N*-Enoyl[2,3] and *N*-acyl[4] sultam derivatives are readily prepared using either sodium hydride–acid chloride or triethylamine–acid chloride single-step protocols. Various alternative derivatization procedures that work for the 10,2-camphorsultam auxiliary would also be expected to be effective.

Reactions of *N*-Enoyl and *N*-Acyl Derivatives.

[2 + 4] Diels–Alder Cycloadditions (Alkene → Six-membered Cycloadduct).[2] *N*-Acryloyl-α-methyltoluene-2,α-sultam (**3a**) participates in highly *endo* and C(α)-*re* π-face selective Lewis acid promoted Diels–Alder reactions with cyclopentadiene, 1,3-butadiene and isoprene (eq 2 and Table 1). These levels of induction compare favorably with most alternative auxiliaries, including the 10,2-camphorsultam. However, *N*-crotonyl-α-methyltoluene-2,α-sultam (*ent*-**3b**) reacts with cyclopentadiene with only moderate π-face selectivity (cf. 93% de with 10,2-camphorsultam).

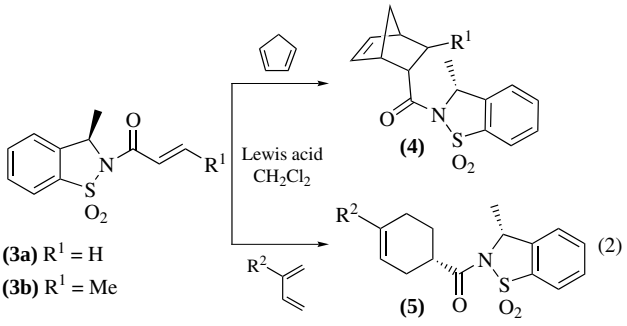


Table 1 Intermolecular Diels–Alder reactions of *N*-enoyl sultams (**3a**) or (**3b**) → **4** and (**3a**) → **5** (eq 2)

Dienophile	Diene	Lewis acid[a]	Temp. (°C)	Time (h)	Adduct	Yield crude (cryst.) (%)	de crude (cryst.) (%)
(**3a**)	Cyclopentadiene	None	25		**4** (R^1 = H)	95[b]	62
(**3a**)	Cyclopentadiene	Me_2AlCl	−98	0.2	**4** (R^1 = H)	97[c] (83)	93 (>99)
(**3a**)	1,3-Butadiene	$EtAlCl_2$	−78	18	**5** (R^2 = H)	79	90
(**3a**)	Isoprene	Me_2AlCl	−78	7	**5** (R^2 = Me)	87	92
ent-(**3b**)	Cyclopentadiene	Me_2AlCl	−78	24	*ent*-**4** (R^1 = Me)	74[d] (58)	59 (>99)

[a] 1.6–2.0 equiv.

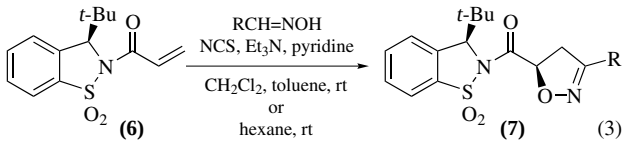
[b] 96% *endo*.

[c] >99% *endo*.

[d] 97% *endo*.

Unusually high *endo* selectivity is observed for the non-Lewis acid-catalyzed reaction of sultam (**3a**) with cyclopentadiene but again the π-face selectivity is only moderate. The corresponding reactions of both α-*t*-butyl- and α-benzyltoluene-2,α-sultams are less selective.

1,3-Dipolar Cycloadditions with Nitrile Oxides (Alkene → Isoxazoline).[3] 1,3-Dipolar cycloaddition reactions of *N*-acryloyl-α-*t*-butyltoluene-2,α-sultam **6** with various nitrile oxides give isoxazolines with extremely high C(α)-*re* π-facial control (eq 3). The levels of selectivity exceed those obtainable with the 10,2-camphorsultam auxiliary and are comparable to the highest levels reported for such cycloadditions.[6] The corresponding reactions of α-methyltoluene-2,α-sultams are less selective.



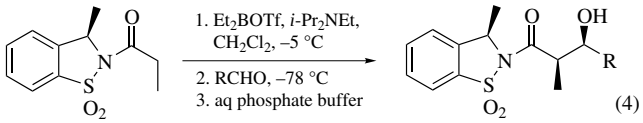
(3)

R = Me*, Et*, *t*-Bu, Ph, CH_2O-*t*-Bu
77–88% (cryst) [90–96% de (crude)]
*using *ent*-**(6)** → *ent*-**(7)**

Acylation, Alkylation, and Aldolization (Acyl Species → α-, β-, or α/β-Functionalized Acyl Product).[3] Alkylation reactions of sodium enolates of various *N*-acyl-α-methyltoluene-2,α-sultams with selected (both "activated" and "nonactivated") alkyl iodides and bromides proceed with good C(α)-*re* stereocontrol (90–99% de). Analogous acylations with various acid chlorides can also be performed, giving β-keto products (97–99% de). Selective reduction of these latter products with zinc borohydride (chelate controlled, 82.6–98.2% de) or N-Selectride (nonchelate controlled, 95.8–99.6% de) can provide *syn*- and *anti*-aldol derivatives, respectively.[3]

Syn-aldol derivatives may also be obtained directly from boryl enolates of the same *N*-acyl-α-methyltoluene-2,α-sultams by condensation with aliphatic and aromatic aldehydes (eq 4).[3,7] The high C(α)-*si* topicity of these reactions parallels but exceeds that when using the 10,2-camphorsultam auxiliary and is the result of an analogous transition state.[3] It is noteworthy, however, that aldolizations of α-methyltoluene-2,α-sultam derivatives generally proceed to completion with just a small excess of aldehyde (1–1.2 equiv, cf. 2–3 equiv when 10,2-camphorsultam mediated). This may be ascribed to the lack of acidic protons α to the SO_2 group in the Saccharine derived auxiliary.

Nondestructive Auxiliary Cleavage. The toluene-2,α-sultam auxiliaries are even more readily cleaved from derivatives than the



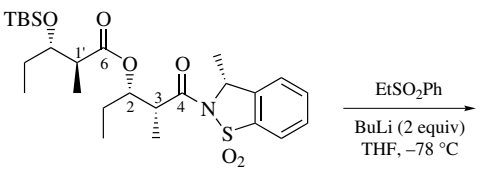
(4)

R = Me, *i*-Pr, *i*-Bu, Ph
71–84% (cryst); [R = *i*-Pr, 95% (FC)]
(>99% of crude)

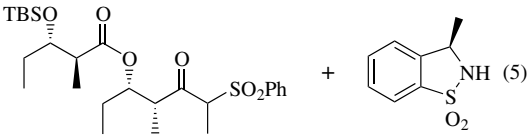
10,2-camphorsultam auxiliary. Following *N*-acyl bond cleavage, simple extraction and crystallization usually effect almost quantitative recovery of enantiomerically pure auxiliary which may be re-used if desired.

Enantiomerically pure carboxylic acids are routinely obtained from *N*-acylsultams by hydrogen peroxide assisted saponification with lithium hydroxide in aqueous THF.[2,4] Alternatively, transesterification can be effected under 'neutral' conditions in allyl alcohol containing titanium tetraisopropoxide, giving the corresponding allyl esters which can be isomerized/hydrolyzed with Wilkinson's catalyst (chlorotris(triphenylphosphine)rhodium(I)) in EtOH–H_2O. This provides a convenient route to carboxylic acids containing base-sensitive functionality.[8] Primary alcohols are obtained by treatment with L-Selectride (lithium *Tri-s*-butylborohydride) in THF at ambient temperature.[3]

The α-methyltoluene-2,α-sultam auxiliary is also displaced by a variety of dilithiated alkyl phenyl sulfones.[7,9] This unique procedure provides direct access to synthetically useful β-oxo sulfones which may be further functionalized or simply subjected to reductive desulfonation to give alkyl ketones. A particularly striking use of this method is the preparation of β-oxo sulfone **8**, a key intermediate in a concise synthesis of (−)-semicorole (eq 5).[7] Remarkably, the $MeCLi_2SO_2Ph$ reagent attacks selectively the C(4)-imide C=O group in preference to the C(6)-ester C=O group and no epimerization occurs at C(3) or C(1′).



[(–)-semicorole numbering]



(5)

(8) 72% (FC) 89% (FC)

Related Reagents. 10,2-Camphorsultam; 10-Dicyclohexylsulfonamidoisoborneol; 2-Hydroxy-1,2,2-triphenylethyl Acetate; (*4S,5S*)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline; (S)-4-Benzyl-2-oxazolidinone.

1. Ganem, B. *Chemtracts–Org. Chem.* **1990**, 435.
2. (a) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015.(b) Oppolzer, W.; Seletsky, B. M.; Bernardinelli, G. *Tetrahedron Lett.* **1994**, *35*, 3509.
3. Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett.* **1991**, *32*, 4893.
4. Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019.
5. Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117.
6. Curran, D. P.; Jeong, K. S.; Heffner, T. A.; Rebek, J., Jr., *J. Am. Chem. Soc.* **1989**, *111*, 9238.
7. Oppolzer, W.; Rodriguez, I. *Helv. Chim. Acta* **1993**, *76*, 1275.
8. Oppolzer, W. Lienard, P. *Helv. Chim. Acta* **1992**, *75*, 2572.
9. Oppolzer, W.; Rodriguez, I. *Helv. Chim. Acta* **1993**, *76*, 1282.

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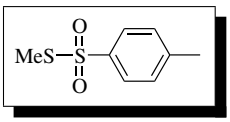
Methyl *p*-Toluenethiosulfonate[1]



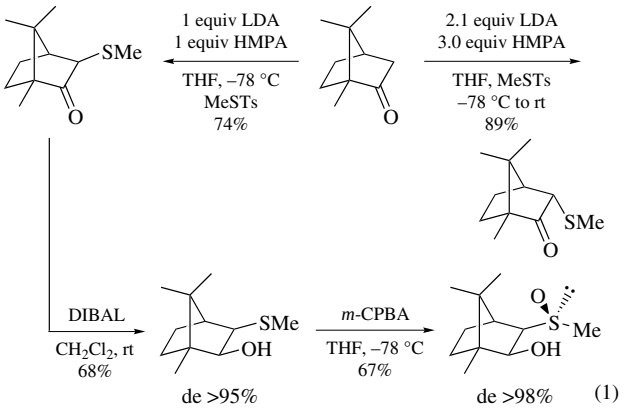
[4973-66-4] $C_8H_{10}O_2S_2$ (MW 202.32)
InChI = 1/C8H10O2S2/c1-7-3-5-8(6-4-7)12(9,10)11-2/h3-6H, 1-2H3
InChIKey = YSAGJMNZJWNJOL-UHFFFAOYAO

(methylsulfenylating agent for formation of useful intermediates which have many applications)

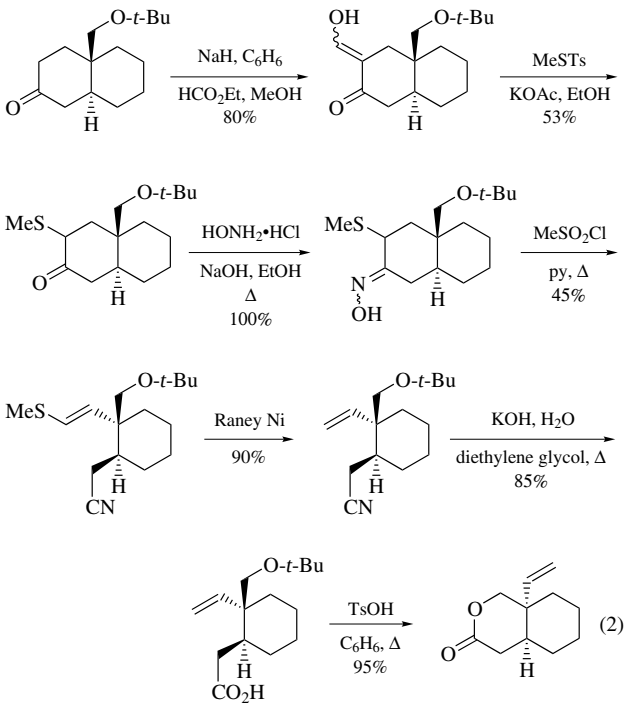
Alternate Name: methyl thiotosylate.
Physical Data: mp 58 °C.
Form Supplied in: white solid.
Preparative Method: prepared by methylation of sodium *p*-toluenethiosulfonate with dimethyl sulfate (65%).[2]

Optically Active Methyl Sulfoxide Derived from Camphor. (+)-Camphor is converted by methylsulfenylation of the lithium enolate with methyl *p*-toluenethiosulfonate (MeSTs) into *exo*-3-(methylthio)camphor, which upon reduction with diisobutylaluminum hydride gives the corresponding *exo*-(methylthio)isoborneol. Oxidation of the sulfide with *m*-chloroperbenzoic acid gives optically pure *exo*-3-(methylsulfinyl)isoborneol (eq 1).[3]

Interestingly, use of excess lithium diisopropylamide and hexamethylphosphoric triamide allows exclusively thermodynamic *endo*-3-(methylthio)camphor formation. The alternative methylsulfenylating agent dimethyl disulfide is not suitable for this highly stereoselective transformation since it gives a mixture of *exo*/*endo* sulfides in low yield. The method is elaborated for use of allyl *p*-toluenethiosulfonates which furnish optically pure *exo*-3-(allylsulfinyl)isoborneols. The derived dianions of these isoborneols undergo diastereoselective conjugate addition reactions with cyclopentenones.[4]

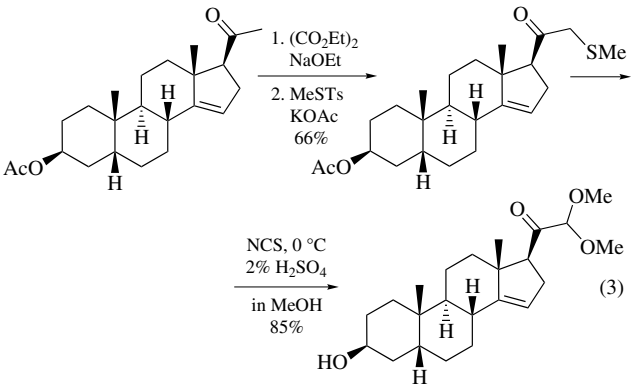


Beckmann Fragmentation of α-Methylsulfenyl Oximes. It is known that a second-order Beckmann fragmentation is favored by introduction of a methylsulfenyl group α to the oxime group.[5] The termini of the bond that is cleaved are obtained in different oxidation states which can be manipulated for further functionalization. MeSTs is used to prepare an α-methylthio ketone, a precursor to the oxime for the fragmentation. An application of this fragmentation is exemplified by a conversion of a cyclohexanone into a δ-valerolactone (eq 2).[6]



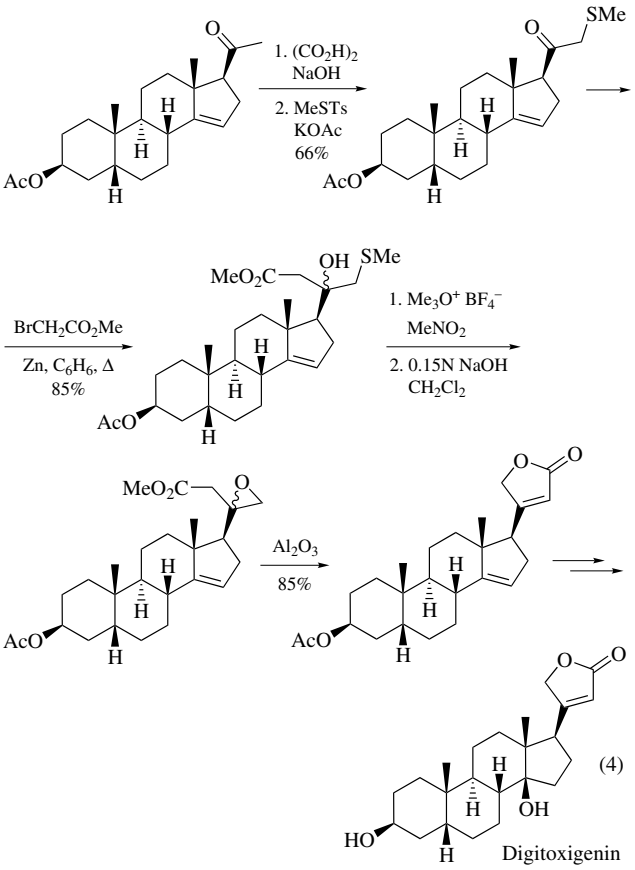
α-Keto Aldehyde from α-(Methylsulfenyl)methyl Ketone. A two-step conversion of a methyl ketone to an α-keto dimethyl

acetal via methylsulfenylation with MeSTs, followed by oxidation with *N*-chlorosuccinimide has been described (eq 3).[7]



(3)

Efficient Synthesis of Cardenolides. A general and efficient method has been described for the synthesis of cardenolides, consisting of (1) α-methylsulfenylation of pregnen-20-one, (2) Reformatsky reaction, and (3) butenolide formation by alumina chromatography of the epoxy ester obtained from the *S*-methylated Reformatsky product (eq 4).[8]



(4)

Related Reagents. Dimethyl Disulfide; Methyl Methanethiosulfonate.

1. Trost, B. M., *Chem. Rev.* **1978**, *78*, 363.
2. Gibson, D. T., *J. Chem. Soc.* **1931**, 2637.
3. Goodridge, R. J.; Hambley, T. W.; Haynes, R. K.; Ridley, D. D., *J. Org. Chem.* **1988**, *53*, 2881.
4. Binns, M. R.; Goodridge, R. J.; Haynes, R. K.; Ridley, D. D., *Tetrahedron Lett.* **1985**, *26*, 6381.
5. (a) Autrey, R. L.; Scullard, P. W., *J. Am. Chem. Soc.* **1968**, *90*, 4917, 4924. (b) Shimizu, Y., *Tetrahedron Lett.* **1972**, 2919.
6. (a) Grieco, P. A.; Hiroi, K., *Tetrahedron Lett.* **1973**, 1831. (b) Grieco, P. A.; Hiroi, K.; Reap, J. J.; Noguez, J. A., *J. Org. Chem.* **1975**, *40*, 1450.
7. Yoshii, E.; Miwa, T.; Koizumi, T.; Kitatsuji, E., *Chem. Pharm. Bull.* **1975**, *23*, 462.
8. Yoshii, E.; Koizumi, T.; Ikeshima, H.; Ozaki, K.; Hayashi, I., *Chem. Pharm. Bull.* **1975**, *23*, 2496.

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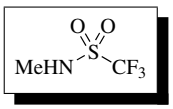
N-Methyltrifluoromethanesulfonamide

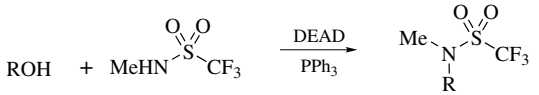


[34310-29-7] $C_2H_4F_3NO_2S$ (MW 163.14)
InChI = 1/C2H4F3NO2S/c1-6-9(7,8)2(3,4)5/h6H,1H3
InChIKey = IJOCNCZJDBTBIP-UHFFFAOYAQ

(methylamine derivative found to react with alcohols under Mitsunobu conditions to give derivatized secondary amines)

Physical Data: bp 90–94 °C/20 mmHg.[1]
Solubility: sol THF, chloroform, methylene chloride.
Form Supplied in: clear liquid.
Preparative Method: prepared from methylamine and trifluoromethanesulfonic anhydride as follows. Methylamine (25.5 g, 0.5 mol) is added to chilled (−70 °C) dichloromethane (250 mL). A solution of triflic anhydride (28.2 g, 0.1 mol) in dichloromethane (20 mL) is added dropwise and the mixture is stirred at −70 °C for 3 h. The mixture is washed with 1N HCl (2 × 250 mL) and the organic layer is separated and dried ($MgSO_4$). The solvent is removed at atmospheric pressure by slow distillation through a column (500 cm × 20 cm) packed with glass helices (product codistills with solvent and evaporation on a rotary evaporator gives very low yields). The residue is distilled to give 9.3 g (57%) of a clear liquid, bp 95–98 °C/30 mmHg.

Secondary Amines. Alcohols react with this compound in THF under Mitsunobu conditions to give derivatized secondary amines.[2] The reaction proceeds with inversion of configuration (eq 1).[2]



(1)

1. Trepka, R. D.; Harrington, J. K.; Beliale, J. W., *J. Org. Chem.* **1974**, *39*, 1094.

2. Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R., *Tetrahedron Lett.* **1990**, *31*, 3417.

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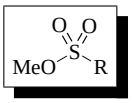
Marion Merrell Dow, Cincinnati, OH, USA

Methyltrifluoromethanesulfonate



(R = CF_3)
[333-27-7] $C_2H_3F_3O_3S$ (MW 164.12)
InChI = 1/C2H3F3O3S/c1-8-9(6,7)2(3,4)5/h1H3
InChIKey = OIRDBPQYVWXNSJ-UHFFFAOYAL
(R = F)
[421-20-5] CH_3FO_3S (MW 114.11)
InChI = 1/CH3FO3S/c1-5-6(2,3)4/h1H3
InChIKey = MBXNQZHITVCSLJ-UHFFFAOYAW

(powerful methylating agents[1,2])

Alternate Name: R = CF_3, methyl triflate; R = F, Magic Methyl.

Physical Data: methyl triflate: bp 99 °C, mp −64 °C, *d* 1.50 g cm^{-3}. Methyl fluorosulfonate: bp 92 °C, mp −92.5 °C, *d* 1.45 g cm^{-3}.

Solubility: both reagents are miscible with all organic solvents, but react with many. They are only sl sol water, but hydrolyze rapidly as they dissolve. Useful inert solvents are CH_2Cl_2, SO_2, sulfolane, nitromethane, Me_2SO_4, and Me_3PO_4.

Form Supplied in: methyl triflate (MeOTf) is available as a colorless liquid. Methyl fluorosulfonate ($MeOSO_2F$) was formerly available as Magic Methyl™ but has been withdrawn (see below).

Analysis of Reagent Purity: MeOTf gives a singlet in ^1H NMR at δ 4.18, with ^{13}C absorption at δ 61.60 and 119.32 (q), and a ^{19}F shift of 75.4 ppm. $MeOSO_2F$ absorbs at δ 4.19 in ^1H NMR (J_{HF} ; 0.4 Hz or less), with ^{13}C absorption at δ 62.45, and a ^{19}F shift of −31.2 ppm. ^{33}S and ^{17}O NMR data have been reported for both compounds.[9]

Preparative Methods: both reagents are prepared[3,4] by distilling an equimolar mixture of the corresponding acid with dimethyl sulfate in an all-glass apparatus with a short Vigreux column. They may be dried by standing over fused K_2CO_3 and redistillation. trifluoromethanesulfonic acid and flurosulfuric acid are both available, and are comparably priced.

Handling, Storage, and Precaution: both reagents are extremely hazardous. All possible precautions should be taken to avoid inhalation or absorption through the skin. A fatality has occurred with $MeOSO_2F$ through inhalation of the vapors leading to pulmonary edema.[5] Dexamethasone isonicotinate (Auxiloson® spray) has been recommended as a first aid in the treatment of such pulmonary irritation.[5] The oral LD_{50} of $MeOSO_2F$ is 112 mg/kg in mice, and an LC_{50} for 1 h exposure for rats between 5 and 6 ppm has been reported; severe eye irritation was noted.[6] It is very unlikely[7] that MeOTf is less dangerous, but no data on toxicity have been reported. Both materials are extremely destructive to the tissue of the mucous membranes and upper respiratory tract, eyes, and skin. Inhalation may be fatal as a result of spasm, inflammation, and edema of the larynx and bronchi, chemical pneumonitis, and pulmonary edema. Use in a fume hood.

The reagents are stable in glass when dry, but storage of $MeOSO_2F$ in bottles with ground glass joints should be avoided as these slowly become fused. It is reported[8] that $MeOSO_2F$ after storage over CaH_2 for two weeks contained 17% Me_2SO_4.

Original Commentary

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University of Bristol, Bristol, UK

General Reactivity. MeOTf and $MeOSO_2F$ are two of the most powerful reagents for methylation and are more reactive by a factor of $\sim 10^4$ than iodomethane and Me_2SO_4.[1,2] The only reagents which are substantially more powerful are methyl fluoride–antimony(V) fluoride and related reagents[10] and the dimethylhalonium ions; these reagents pose more severe handling problems. The reactivity of MeOTf and $MeOSO_2F$ is not effectively enhanced by addition of Lewis acids. Thus addition of antimony(V) chloride to $MeOSO_2F$ and dimethyl sulfone led to complexation of the sulfone rather than methylation;[11] it is also reported that addition of $SbCl_5$ leads to formation of MeCl.[12]

The qualitative reactivity of some methylating agents toward a range of functional groups is shown in tabular form (Table 1).[1] Few quantitative data are available, but MeOTf and $MeOSO_2F$ are only a little less reactive than the trimethyloxonium ion, with the dimethoxycarbenium ion probably somewhat more reactive again. Substitution rates with various nucleophiles are reported to be in the order: $Me_3O^+ > MeOTf > MeOSO_2F > MeOClO_3$, with rate ratios of 109:23:8:6:1.0 for reaction with acetonitrile at 0 °C.[13,14] Methyl perchlorate, an explosion hazard, therefore never offers a practical advantage. Our experience is that the relative rates for MeOTf and $MeOSO_2F$ rarely differ by more than a factor of 2–5.

It is noteworthy that neither MeOTf nor $MeOSO_2F$ shows any reactivity on their own in Friedel–Crafts methylation reactions even with highly reactive substrates (Me_3O^+ ion is similar). Reaction has been observed in the presence of protic or Lewis acids.[15] Olah has recently suggested that this reactivity is associated with generation of superelectrophiles by further protonation.[16] $MeOSO_2F$ has been reported to react as a methylsulfonylating agent towards phenol and anisole,[17] but this alternative reactivity is usually not significant.

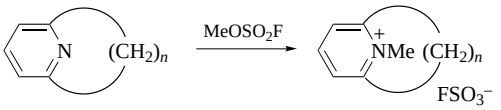
The alkylation reactions of MeOTf and $MeOSO_2F$ are discussed according to the atom alkylated. To avoid unnecessary repetition, reactions can be assumed to use MeOTf unless $MeOSO_2F$ is specified. Historically, $MeOSO_2F$ was mainly used up until about 1980, but MeOTf has since become the reagent of choice. In the great majority of cases these reagents can probably be used interchangeably.

Table 1 Reactivity[a] of methylating agents towards functional groups

	Approx. pK_a[18]	MeI	Me_2SO_4	$MeOSO_2F$ (MeOTf)	Me_3O^+	$HC(OMe)_2^+$	Me_2Cl^+
Me_3N	9	+	+	++	++	++	++
Pyridine	5	+	+	++	++	++	++
Me_2S	1	+	+	++	++	++	++
Me_2SO	0	+	+	+	+	+	++
$HCONMe_2$	0	−	+	+	+	+	++
MeCN	−10	−	−	+	+	+	+
Me_2O	−5	−	−	+	(+)	+	+
PhCHO	−6	−	−	+	−	+	+
R_2CO	−6	−	−	±	−	±	+
Lactone	−7	−	−	+	−	+	+
Ester	−7	−	−	(+)	−	+	+
MeI	?	−	−	(+)	−	(+)	+
$MeNO_2$	−10	−	−	−	−	−	+
Me_2SO_2	−10	−	−	−	−	−	+

[a] Key: ++ methylation occurs and may be strongly exothermic; + methylation occurs; − little reaction; (+) equilibrium transfer reaction; ± reaction is complex.

Alkylation at Nitrogen. Most amines react violently with MeOTf or $MeOSO_2F$, and only those with severe steric hindrance or conjugated with strong electron-withdrawing groups really require the use of these reagents. Of derivatives with sp^3 nitrogen, diisopropylamine, *N*,2,2,6,6-pentamethylpiperidine, and 1,8-bis(dimethylamino)naphthalene (Proton Sponge™) can all be quaternized by $MeOSO_2F$, and *N*,*N*,2,6-tetramethylaniline reacts on heating.[1] However, it has been reported that *i*-Pr_3N does not react with $MeOSO_2F$.[19] 2,6-lutidine reacts exothermically with $MeOSO_2F$ at room temperature, and 2,6-dimethoxycarbonylpyridine can be quantitatively quaternized.[1] A range of [*n*](2,6)-pyridinophanes have been methylated with $MeOSO_2F$, with *n* as small as 6 (eq 1).[20]



(1)

2,6-Di-*tert*-butylpyridine does not react at normal pressure, and this or 2,6-di-*t*-butyl-4-methylpyridine (synthesis[21]), are often used in applications which require base (see below). Note that 2,6-di-*t*-butylpyridine can be alkylated under high pressure with $MeOSO_2F$ to give >90% of the methylation product when water is carefully excluded.[22]

Simple imines, such as benzylideneaniline, react readily. The *N*-methylation of imine and amidine derivatives of amino acid esters, followed by hydrolysis, has been used as a method for the preparation of *N*-alkylated amino acids with minimal racemization.[23] A convenient synthesis of *N*-methyl nitrones has been developed by alkylation of OTMS oximes with MeOTf, followed by treatment with fluoride ion.[24]

Besides the pyridine derivatives already mentioned, most heterocyclic nitrogens can be alkylated. Aspects of the quaternization of heteroaromatics have been recently reviewed.[25] With respect to the limits of reactivity, it is interesting that dimethylation of 2-phenyl-4,6-dimethylpyrimidine could only be achieved with trimethyloxonium tetrafluoroborate; $MeOSO_2F$ only gave monoalkylation.[26] 2-Benzoylbenzothiazole can be *N*-alkylated with $MeOSO_2F$ (but not with MeI) and then acts as an active acylating agent.[27] Formation of an *N*-methylindole from an *N*-ethoxycarbonylindole has been achieved with $MeOSO_2F$.[28]

A number of alkylation products from MeOTf and heterocycles have been advocated as useful intermediates. Thus treatment of 2-substituted thiazoles with MeOTf in acetonitrile, followed by reduction of the salt formed with sodium borohydride/CuO in CH_2Cl_2, leads to aldehydes.[29] 1-(Benzenesulfonyl)-3-methylimidazolium and 1-(*p*-toluenesulfonyl)-3-methylimidazolium triflates have been proposed as efficient reagents for the preparation of aryl sulfonamides and aryl sulfonates.[30] MeOTf alkylates 2,5-oxazoles to give salts which can be reduced by $PhSiH_3$/CsF to give 4-oxazolines, and these provide a route to stabilized azomethine ylides.[31]

A novel synthesis of 2-aryl-4-piperidones by Mannich cyclization of imino acetals, initiated by methylation of the imine, has been described.[32] MeOTf has been used in the generation of a munchnone for cycloaddition.[33] Finally, methylation of 1-lithio-2-*n*-butyl-1,2-dihydropyridine with MeOTf gives 2-butyl-5-methylpyridine in 42% yield.[34]

Nitriles, with sp hybridized nitrogen, are unreactive to MeI or Me_2SO_4, but are readily methylated by $MeOSO_2F$,[1] MeOTf,[35] or oxonium ions. Nitrilium salts have been shown to have a number of useful applications. The reduction of nitrilium salts by $NaBH_4$ in alcohols leads first to iminoethers and subsequently to amines.[36] Reduction of *N*-alkylnitrilium ions by organosilicon hydrides gives *n*-alkylaldimines, and thus provides a route to aldehydes from nitriles.[37] Nitrilium triflate salts have been shown to be useful reagents for the synthesis of ketones and ketenimines by electrophilic substitution of reactive aromatics, and also provide good routes to amidinium, imidate, and thioimidate salts.[35] Reaction with 2-amino alcohols gives oxazolidines.[38] Synthesis of either 5-substituted 1-methyl-1*H*-tetrazoles or 3,5-disubstituted 1,4-dimethyltriazolium salts from *N*-methylnitrilium triflate salts can be controlled in reactions with $(Me_2N)_2C{=}NH_2{}^+N_3{}^-$.[39] Reaction of nitrilium ions with alkyl azides gives 1,2,3-trisubstituted tetrazolium salts.[40] These can be deprotonated to highly reactive 2-methylenetetrazoles.[41]

Amides are alkylated largely on oxygen, as expected (see below), although some *N*-alkylation can be seen by NMR.[1] *N*-Alkylation is more apparent with carbamates (see the section on

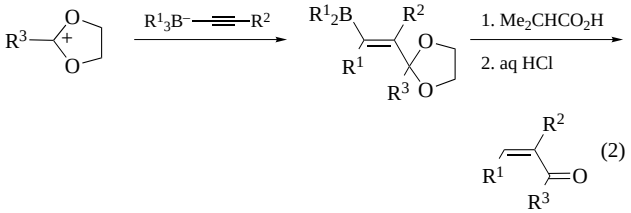
ambident nucleophiles). *N,N*-Dimethylmethanesulfonamides can be *N*-alkylated ($MeOSO_2F$) to provide salts which are effective reagents for mesylation.[42] *N,N*-Dimethylsulfamate esters react with $MeOSO_2F$ to give trimethylammoniumsulfate esters, which rapidly give methyl esters unless the O-group is aryl, showing that $Me_3N^+SO_3^-$ is a very powerful leaving group.[43] $Me_3N^+SO_2OPh$ reacts with nucleophiles at either the sulfur or a methyl carbon atom.[44]

Azo compounds, which do not react with methyl iodide, can be *N*-methylated by $MeOSO_2F$.[45]

A steroidal oxaziridine was converted ($MeOSO_2F$) to an oxaziridinium salt which showed oxidizing properties.[46]

Alkylation at Oxygen. Most neutral functionalities with lone pairs on oxygen are not alkylated by MeI or Me_2SO_4 but do react with MeOTf or $MeOSO_2F$, although not all such reactions are preparatively useful.[1,2] Ethers react reversibly, and the ultimate product depends on the conditions. Thus good yields of the oxonium ion can be obtained from reaction of THF with stoichiometric amounts of MeOTf, but the use of catalytic amounts leads to polymerization. Cationic ring opening polymerization, initiated by MeOTf and $MeOSO_2F$ among other reagents, has been extensively investigated and recently reviewed.[47]

Reaction of $MeOSO_2F$ with 2-methoxyethyl carboxylates gives 2-alkyl-1,3-dioxolanium ions.[1] The reaction of these ions with trialkylalkynylborate anions provides versatile and direct routes to (*Z*)-α,β-unsaturated ketones (eq 2). Specifically protected 1,3-diketones and other ketonic species can also be prepared from the intermediates.[48]

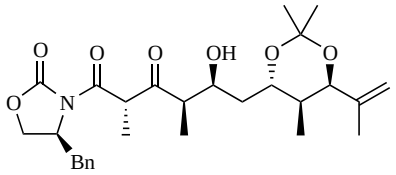


(2)

Almost all carbonyl functions can be methylated. Enolizable aldehydes and ketones usually lead to complex mixtures, probably because of deprotonation to enol ethers, followed by reaction of these with the electrophilic species in the reaction mixture. Nonenolizable aldehydes and ketones give methoxycarbenium ions cleanly, and the relative thermodynamic stabilities of these have been assessed via pairwise equilibrations.[49] Most esters only generate low equilibrium concentrations of dialkoxycarbenium ions, but lactones are readily alkylated.[1]

Amides, carbamates, and ureas are rapidly alkylated, usually on carbonyl oxygen (see the section on ambident nucleophiles). Alkylation of amides with MeOT5f in CH_2Cl_2 followed by reduction of the salts provides a route for the selective reduction of amides; esters, nitriles, acetals, and double bonds are left unaffected by this procedure.[50] Alkylation of isoindolin-1-ones and subsequent deprotonation can provide routes to methoxyisoindoles.[51]

Alcohols can be converted to methyl ethers by the use of MeOTf + 2,6-di-*t*-butylpyridine or 2,6-di-*t*-butyl-4-methylpyridine. This procedure was initially developed in the carbohydrate field.[52] Me_3PO_4 provides a good polar solvent for this process.[53] A recent application, in the synthesis directed at lonomycin, was to methylation of the complex alcohol (**1**) without causing retroaldol cleavage.[54]

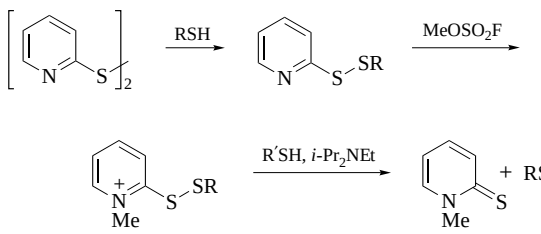


(1)

MeOTf has been reported to effect complete methylation of inositol polyphosphates, P–OMe groups being formed as well.[55] MeOTf will effect *O*-alkylation at the anomeric center, but the stereochemistry is affected by the presence of a crown ether.[56] Reaction of Meisenheimer complexes with $MeOSO_2F$ can lead to capture of the anion as a nitronate ester.[57]

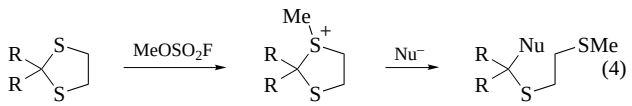
Alkylation at Sulfur and Selenium. Dialkyl and most arylalkyl sulfides are readily converted into sulfonium salts.[1] Cyclic sulfides, especially dithiolanes, react somewhat faster.[58] Reaction of disulfides with MeOTf gives Me_2SSMe^+ OTf^-; this salt, with triphenylphosphine, reacts with alkenes in a stereo- and regioselective fashion and the products can be converted into vinylphosphonium salts.[59] Thione groups are also alkylated even when electronegative groups are present. Thus 4,5-bis(trifluoromethyl)-1,3-dithiolane-2-thione was converted into a methylated salt.[60] Sulfoxides are *O*-alkylated,[1] and formation of various oxa- and azasulfonium ions has been reported, up to and including triazasulfonium salts.[61] Alkylation of R_2SO with $MeOSO_2F$, followed by reduction with sodium cyanoborohydride, leads to sulfides.[62]

Reaction of MeOTf with the product from P_2S_5/Na_2CO_3 ($Na_2P_4S_{10}O$) gave a useful electrophilic thionation reagent.[63] $MeOSO_2F$ has been used in the conversion of thiols to reactive sulfenating agents (eq 3).[64]



(3)

Methylation of dithioacetals by $MeOSO_2F$, followed by reaction with various nucleophiles, has been used for the removal of this protecting group or its conversion into other protecting groups, e.g. acetals (eq 4).[65–68]



(4)

The reaction of the sulfonium intermediate with alcohols leads to their protection as hemithioacetals.[69] Treatment of thioglycosides with MeOTf gives an efficient glycosylating agent,[70] and pyruvic acetal formation from a pyruvyl thioacetal has been achieved in a reaction catalyzed by MeOTf (amongst other electrophiles).[71]

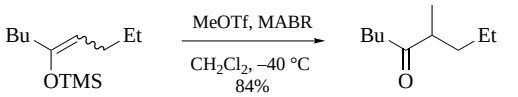
Alkenes can be prepared by methylation of selenides by $MeOSO_2F$ and treatment of the selenonium ions formed with potassium *tert*-butoxide.[72]

Alkylation at Phosphorus. Phosphines and phosphites undergo easy quaternization. Thus methylation of tris(2,6-dimethylphenoxy)phosphine with MeOTf, followed by treatment of the product with sodium 2,6-dimethylphenoxide, gave methyltetrakis (2,6-dimethylphenoxy)phosphane.[73] Methoxyphosphonium triflates are relatively stable intermediates in Arbuzov reactions.[74] Phosphine oxides and sulfides are alkylated. *S*-Methylation of chiral phosphine sulfides, followed by treatment with hexamethylphosphorous triamide, has been advocated as a general synthesis of optically active phosphines.[75]

Ambident Nucleophiles. Amides and related functional groups can be alkylated on oxygen or nitrogen and, as has been noted already, alkylation on carbonyl oxygen normally predominates. In the case of carbamates, *O*-alkylation by $MeOSO_2F$ can be faster, but *N*-alkylation predominates at equilibrium.[76] It has been noted that methylation of secondary amides and thioamides occurs at the protonless heteroatom in the major tautomer.[77] The ionic products of these reactions can be deprotonated to give synthetically useful products, e.g. imidates,[78] but excess $MeOSO_2F$ should be removed before treatment with base.[77]

Reaction of most enolates with MeOTf or $MeOSO_2F$ is always likely to be kinetically controlled. There does not appear to have been a definitive study, but *O*-alkylation is the normal outcome. *O*-Alkylation of a bicyclodecatrienone by $MeOSO_2F$ is enhanced by the use of polar solvents like HMPA.[79] *O*-Alkylation of enolates of appropriate cyclohexadienones by MeOTf has been used to generate various 3a*H*-indenes.[80] A ketene acetal is formed by exclusive *O*-alkylation of the sodium enolate of isopropyl bis(pentachlorophenyl)acetate by MeOTf.[81]

Alkylations at Carbon. In an important recent development, primary α-alkylation of carbonyl compounds under nonbasic conditions has been achieved (eq 5) by alkylation of silyl enol ethers with MeOTf and other primary alkyl triflates, catalyzed by methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide (MABR).[82]



(5)

Related Reagents. Dimethoxycarbenium Tetrafluoroborate; Dimethyliodonium Hexafluoroantimonate; *O*-Methyldibenzofuranium Tetrafluoroborate; Triethyloxonium Tetrafluoroborate.

First Update

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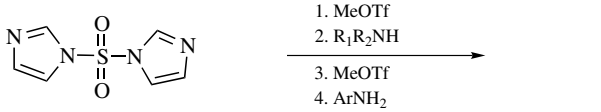
Alkylation at Nitrogen. MeOTf can readily react with many types of nitrogen containing compounds under mild conditions. Recent developments of MeOTf mediated *N*-alkylation focused on the utility of *N*-quaternary intermediates.

N-Methylation confers a positive charge on nitrogen atoms, thus converting them into good leaving groups. *N*,*N*′-Sulfuryldiimidazole was activated towards displacement by *N*-methylation with MeOTf. The imidazolium group of the resulting triflate salt was then displaced with a variety of amines and anilines to afford unsymmetrical sulfonylureas in excellent yield (eq 6).[83] Quaternization of an *N*-(2-pyridyl)tosylamide in a protected amino alcohol by MeOTf, followed by base treatment provided a mild method for removing the pyridine moiety without epimerization (eq 7).[84] The reaction of a sulfonylated bicyclic amine with excess MeOTf followed by treatment with sodium amalgam led to an unsaturated cyclic amine in 71% yield (eq 8).[85] Intramolecular regioselective epoxidation of a less electron-rich alkene in a nonconjugated diene was achieved by the oxaziridinium salts formed from oxaziridines and MeOTf (eq 9).[86] MeOTf can also be used for solid phase synthesis. An aminoxy functionalized resin was utilized in traceless solid phase syntheses of amines. Basic cleavage following MeOTf alkylation of the nitrogen afforded tertiary methylamines in high purity.[87,88]



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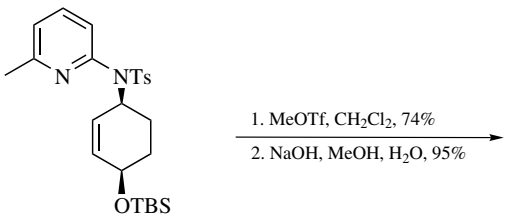

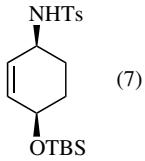

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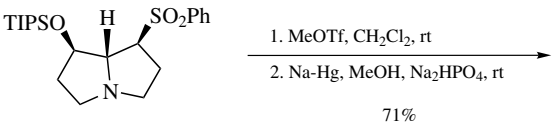

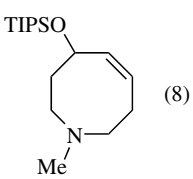

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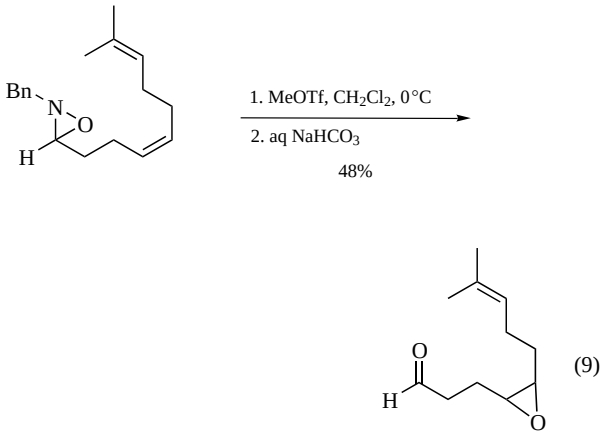
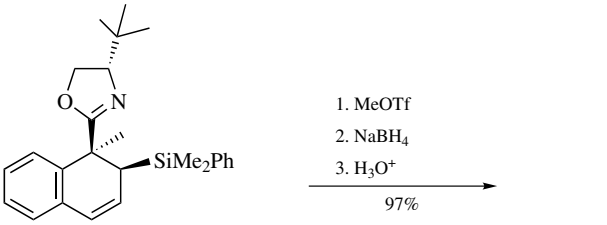
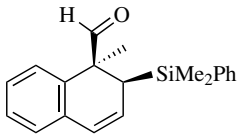


(9)

Quaternization of the nitrogen atom in a heterocyclic system can activate the ring towards addition reactions. An oxazoline moiety was converted to an aldehyde in 97% overall yield by alkylation of oxazoline with MeOTf, reduction with sodium borohydride, and hydrolysis of the resulting aminal (eq 10).[89] Alternatively, treatment of an *N*-methylated oxazolium triflate with a Grignard reagent followed by aqueous acid produced a ketone.[90] Reaction of alkenyl oxazoles with MeOTf induced spontaneous intramolecular [4 + 2] cycloaddition at room temperature leading to a hydroindole or a hydroisoquinoline after reduction by sodium borohydride (eq 11).[91]





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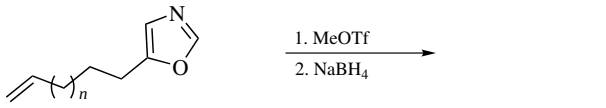
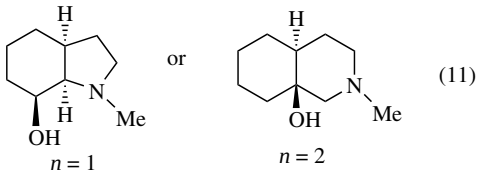


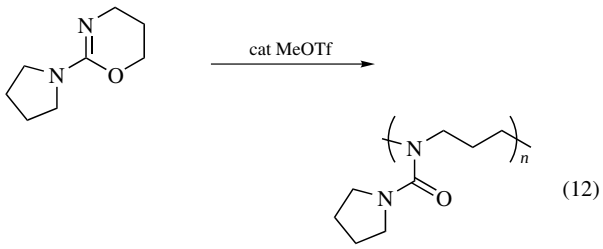
n = 1 or 2



n = 1 *n* = 2

(11)

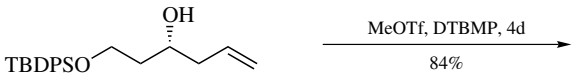
MeOTf, as an initiator, can promote cationic ring-opening polymerization of a six-membered cyclic pseudourea via *N*-methylation, producing poly(*N*-carbamoylimino) trimethylene (eq 12). The reaction with alkyl halides as promoters gave a polymer mainly consisting of 1,3-diazin-2-one-1,3-diylalkylene unit.[92]

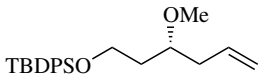


(12)

Due to its superior reactivity, ^{11}C labeled MeOTf has been introduced as a highly reactive alternative to ^{11}C labeled methyl iodide in preparation of ^{11}C radiopharmaceuticals through methylation of amines.[93]

Alkylation at Oxygen. Alcohols can be methylated by MeOTf in the presence of sterically hidered bases such as di-*tert*-butyl-4-methyl-pyridine (DTBMP),[94] or with the aid of organolithium reagents.[95] A secondary alcohol was converted to methyl ether in high yield using MeOTf and DTBMP without affecting a *tert*-butyldiphenyl silyl (TBDPS) ether (eq 13).[96] Significant TBDPS migration to the secondary hydroxyl group was observed when more basic conditions (NaH with MeI) were employed. *O*-Methylation of tylosin derivatives with excess MeOTf and DTBMP gave the 3-methyl ether in 49% yield in the presence of adjacent acetoxy groups (eq 14). Reactions in other solvents, and the use of MeI-Ag_2O, led to migration of the acetyl group or partial deacetylation to give a complex reaction mixture.[97] Sterically hindered alcohols also could be methylated with MeOTf, although they required more forcing conditions (*n*BuLi, MeOTf) (eq 15).[98,99]





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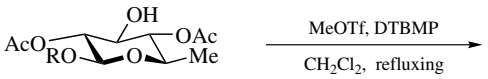
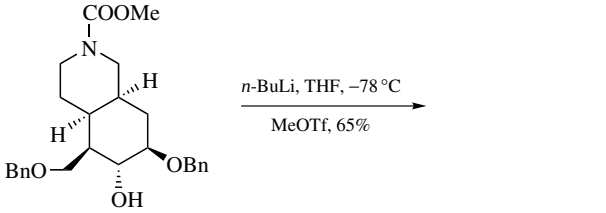


(14)

R = mycaminosyltylonolide alygcon

MeOTf has been reported to effect the dealkoxylation of a perfluoroalkyltrialkoxyboronate to generate the corresponding boronic ester.[100] Conversely, an alkenyl boroxycarbene complex was reacted with MeOTf to remove the borane-based chiral auxiliary yielding a Fischer carbene complex.[101] *tert*-Amide substituted oxetanes rearranged in anhydrous nitrobenzene at 150 °C with a catalytic amount of MeOTf to produce ester-substituted azetidines (eq 16).[102] Other acids such as boron trifluoride etherate, trifluoromethanesulfonic acid, and benzylthiolanium hexafluoroantimonate led to low yields of the desired azetidines.



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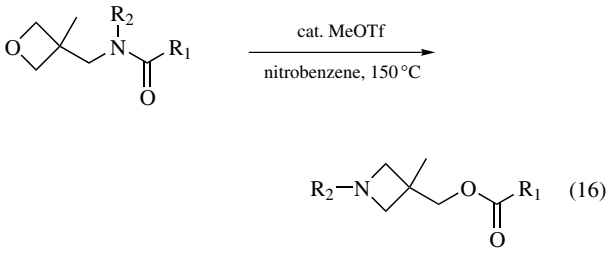
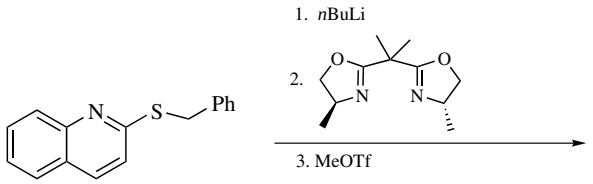


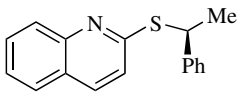
(16)

Alkylation at Carbon. MeOTf can serve as a carbanion alkylating reagent giving one carbon extended homologs. Methylation of the sodium salt of a terminal alkyne with MeOTf afforded a propynyl intermediate in excellent yield.[103] It has been reported that alkylation of ketone enolates with MeOTf in ether or hexane proceeded in high yields without the exchange products, that occurred when methyl halides or methyl sulfate were used.[104] Lithiation of 2-methyloxazoles with lithium diethylamide followed by treatment with MeOTf resulted in the selective formation of 2-ethyl oxazoles.[105] The usage of lithium diethylamide was crucial to achieve high selectivity, as the conjugated acid, diethylamine, led to formation of the most stable carbanion. The nature of the electrophile and substrate was found to greatly affect the selectivities of alkylation.[106]

Methylation by MeOTf can also be carried out asymmetrically. Treatment of α-lithio benzyl 2-quinolyl sulfide with MeOTf in the presence of a bis(oxazoline) as an external chiral ligand yielded chiral 1-phenylethanethio quinolyl sulfide (eq 17).[107] Lithiation adjacent to nitrogen of chiral 3,4-substituted piperidines and pyrrolidines followed by diastereoselective substitution with MeOTf offered general routes to 2,4,5- and 2,4,5,6-substituted piperidines as well as 2,3,4- and 2,3,4,5-substituted pyrrolidines.[108]

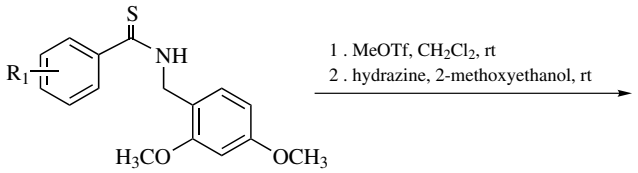
Alkylation at Sulfur and Selenium. Thioamides can be converted to the corresponding thioimidates via alkylation with MeOTf, which is very useful for introducing different functional groups at the thiocarbonyl carbon. Direct conversion of a thioamide to the amidrazone by heating with hydrazine was not successful, but the thioimidate readily reacted with hydrazine at room temperature to afford the desired product (eq 18).[109] It has been reported that thioiminium salts generated in situ from thioamides and MeOTf can be used to construct carbon–carbon bonds by sequential reaction with organolithium and Grignard reagents. A variety of tertiary propargylamines were conveniently synthesized by this protocol (eq 19).[110] Treatment of selenoamides with MeOTf, followed by reaction with lithium acetylides furnished β-methylselenenyl α, β-unsaturated ketones in high yield. These reaction proceed with high stereoselectivity to give exclusively *Z*-isomers.[111]

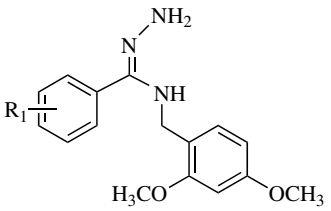




(17)

85% yield, 78% ee





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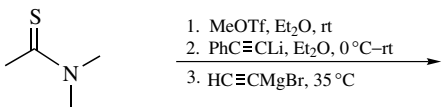
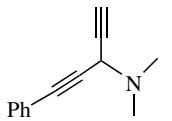
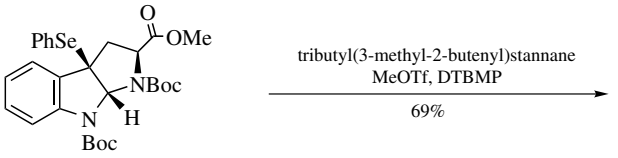
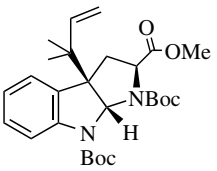




(19)

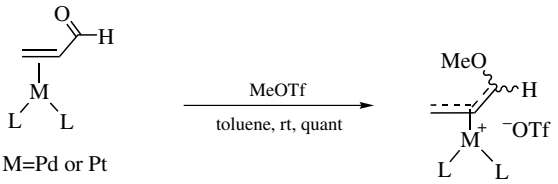
Thioethers and selenoethers can be displaced with various nucleophiles after methylation by MeOTf. This has been used extensively in the carbohydrate synthesis field (see the section on glycosylation). A phenylselenide moiety was substituted stereospecifically by an alkyl stannane following MeOTf activation in the construction of a C−C bond between two quaternary carbon centers (eq 20).[112]





(20)

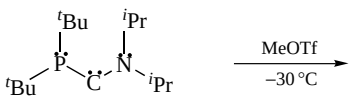
Alkylation of Metal Complexes. MeOTf has been reported to alkylate transition metal complexes on either the metal center or the ligands. The reaction of η^2-acroleinpalladium complexes with MeOTf in toluene at room temperature quantitatively gave a palladium complex with a η^3-methoxyallyl structure, which has been proposed as an important intermediate in several catalytic reactions (eq 21).[113] The replacement of MeOTf with MeI led to oxidative addition, forming methyl metal complexes with concomitant dissociation of the acrolein. The sequential addition of alkyllithium reagents and MeOTf to a series of cyclomanganated 2-phenylpyridine derivatives afforded metallospiralenes.[114,115] *N*-Rhenaimine β-lactams underwent clean demetalation with MeOTf to yield the *N*-methyl-β-lactams.[116] Novel square-planar, terdentate, aryl-substituted pyridine-diimine Rh(I) and Ir(I) triflate complexes were synthesized by treatment of the corresponding chloro complexes with MeOTf to produce a methylated Rh(III) or Ir (III) complex followed by reduction.[117]

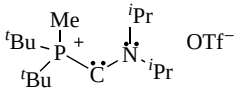


M=Pd or Pt
L=PPh_3 or dppf

(21)

Alkylation at Phosphorus. Bis(trifluoromethyl)phosphines were methylated by MeOTf, yielding the corresponding phosphonium salts, which can be deprotonated using $MeN=P(NEt_2)_3$ leading to the phosphorus ylides.[118] An amino-phosphino carbene was transformed through *P*-methylation with MeOTf into an aminophosphonio carbene, which underwent nucleophilic substitution reactions at the carbene center (eq 22). Various carbenes can be synthesized starting from a single precursor, allowing facile adjustment of electronic and steric effects at the carbene, which can facilitate the study of the structure/catalytic activity relationship for carbine-metal complexes.[119]

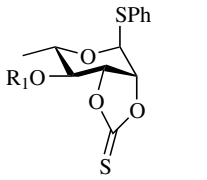


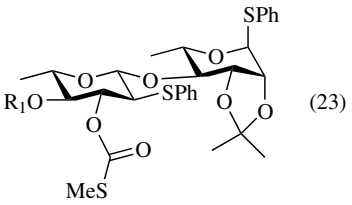


(22)

Phosphine oxides can be efficiently alkylated with MeOTf. Optically active *P*-chirogenic phosphine oxides were reduced with inversion of configuration at the phosphorus atom to yield chiral phosphines by sequential treatment with MeOTf and $LiAlH_4$.[120]

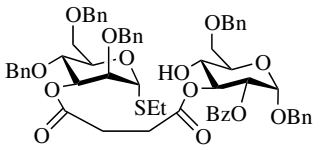
Promoter for Glycosylation. MeOTf is a moderately reactive promoter for thioglycosyl donors, most commonly *S*-methyl or ethyl thioglycosides.[121] MeOTf is less potent than the widely used *N*-iodosuccinimide (NIS) and triflic acid (TfOH)/silver triflate system, therefore an excess of reagent is often required for complete activation. MeOTf can activate a wide array of thioglycosides including glucosamine,[122] mannose,[123] and glucose[124] derivatives with ether-protected thioglycosides being more reactive than the corresponding esters. Complex oligosaccharides can be assembled using MeOTf promoted thioglycoside glycosylation.[125] *O*-Methylation of the glycosyl acceptor hydroxyl group has been observed as a side reaction in the glycosylation of an unreactive thioglycoside with a reactive acceptor. Treatment of phenyl 2,3-*O*-thionocarbonyl-1-thio-α-L-rhamnopyranosides with MeOTf resulted in 1,2-migration and concurrent glycosylation (eq 23).[126] Besides intermolecular glycosylation, MeOTf can also be used to promote the intramolecular aglycon delivery forming the challenging β-mannosyl linkage (eq 24).[125,127]



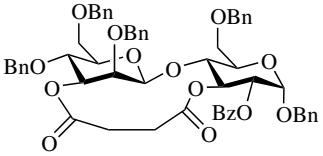


(23)

83%



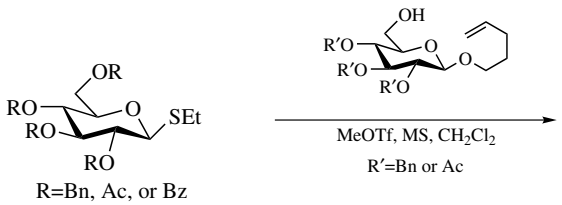
MeOTf, DTBMP
rt, MeCN, 3h
64%

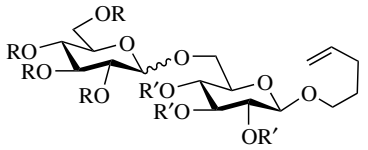


(24)

Due to the high reactivity of MeOTf towards the sulfur atom, MeOTf can chemoseletively activate thioglycosides in the presence of an alkene. This has allowed the development of a chemoselective glycosylation protocol in which a thioglycosyl donor is selectively glycosylated with a glycosyl acceptor bearing an *O*-pentenyl moiety at its anomeric center (eq 25). The resulting oligosaccharide can be further activated enabling rapid

synthesis of complex oligosaccharides.[128] In contrast, the usage of other thiophilic promoter systems such as NIS/TfOH and iodonium (di-γ-collidine) perchlorate led to low yields of the desired oligosaccharide due to competing reaction with the alkene.





95–98% (25)

In addition to thioglycosides, MeOTf can promote the activation of 3-methoxypyridyl *O*-unprotected glycosyl donors,[129] and of *S*-benzoxazolyl glycosides for highly stereoselective 1,2-*cis*-glycosylations.[130]

Due to the possibility of side reactions of acceptors with MeOTf and safety considerations, a more specific promoter, dimethyl (methylthio)sulfonium triflate (DMTST), can be utilized instead of MeOTf; it is produced by mixing MeOTf with dimethyl disulfide.[59]

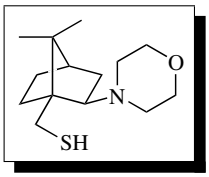
Related Reagents. Methyl Iodide; Methyl Sulfate; 1-Benzenesulfinyl Piperidine; Diphenyl Sulfoxide; Dimethyl(methylthio) Sulfonium Tetrafluoroborate.

1. Alder, R. W., *Chem. Ind. (London)* **1973**, 983.
2. (a) Stang, P. J.; Hanack, M.; Subramanian, L. R., *Synthesis* **1982**, 85. (b) For other reviews of trifluoromethanesulfonates, see: Howells, R. D.; McCown, J. D., *Chem. Rev.* **1977**, *77*, 69 and Stang, P. J.; White, M. R., *Aldrichim. Acta* **1983**, *16*, 15.
3. Ahmed, M. G.; Alder, R. W.; James, G. H.; Sinnott, M. L.; Whiting, M. C., *J. Chem. Soc., Chem. Commun.* **1968**, 1533.
4. Beard, C. D.; Baum, K.; Grakauskas, V., *J. Org. Chem.* **1973**, *38*, 3673.
5. (a) van der Ham, D. M. W.; van der Meer, D., *Chem. Ind. (London)* **1976**, 782. (b) van der Ham, D. M. W.; van der Meer, D., *Chem. Eng. News* **1976**, *54*(36), 5.
6. Hite, M.; Rinehart, W.; Braun, W.; Peck, H., *Am. Ind. Hyg. Assoc.* **1979**, *40*, 600 (*Chem. Abstr.* **1979**, *91*, 84 580d).
7. Alder, R. W.; Sinnott, M. L.; Whiting, M. C.; Evans, D. A.; *Chem. Eng. News* **1976**, *54*(36), 56.
8. Hase, T.; Kivikari, R., *Synth. Commun.* **1979**, *9*, 107.
9. Barbarella, G.; Chatigilialoglu, C.; Rossini, S.; Tugnoli, V., *J. Magn. Reson.* **1986**, *70*, 204.
10. Christie, J. J.; Lewis, E. S.; Casserly, E. F., *J. Org. Chem.* **1983**, *48*, 2531.
11. Minato, H.; Yamaguchi, K.; Miura, T.; Kobayashi, M., *Chem. Lett.* **1976**, 593.
12. Binder, G. E.; Schmidt, A., *Z. Anorg. Allg. Chem.* **1980**, *467*, 197 (*Chem. Abstr.* **1980**, *93*, 196 905m).
13. Kevill, D. N.; Lin, G. M. L., *Tetrahedron Lett.* **1978**, 949.
14. (a) Lewis, E. S.; Vanderpool, S., *J. Am. Chem. Soc.* **1977**, *99*, 1946; (b) Lewis, E. S.; Vanderpool, S., *J. Am. Chem. Soc.* **1978**, *100*, 6421; (c) Lewis, E. S.; Kukes, S.; Slater, C. D., *J. Am. Chem. Soc.* **1980**, *102*, 303.
15. (a) Olah, G. A.; Nishimura, J., *J. Am. Chem. Soc.* **1974**, *96*, 2214; (b) Booth, B. L.; Haszeldine, R. N.; Laali, K., *J. Chem. Soc., Perkin Trans. 1* **1980**, 2887.
16. Olah, G. A., *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767.
17. Kametani, T.; Takanashi, K.; Ogasawara, K., *Synthesis* **1972**, 473.
18. Arnett, E. M., *Prog. Phys. Org. Chem.* **1963**, *1*, 223.
19. Wieland, G.; Simchen, G., *Liebigs Ann. Chem.* **1985**, 2178 (*Chem. Abstr.* **1986**, *104*, 33 742n).
20. Weber, H.; Pant, J.; Wunderlich, H., *Chem. Ber.* **1985**, *118*, 4259 (*Chem. Abstr.* **1986**, *104*, 129 776c).
21. Anderson, A. G.; Stang, P. J., *Org. Synth.* **1981**, *60*, 34.
22. Hou, C. J.; Okamoto, Y., *J. Org. Chem.* **1982**, *47*, 1977.
23. O'Donnell, M. J.; Bruder, W. A.; Daugherty, B. W.; Liu, D.; Wojciechowski, K., *Tetrahedron Lett.* **1984**, *25*, 3651.
24. Le Bel, N. A.; Balasubramanian, N., *Tetrahedron Lett.* **1985**, *26*, 4331.
25. Gallo, R.; Roussel, C.; Berg, U., *Adv. Heterocycl. Chem.* **1988**, *43*, 173.
26. Douglass, J. E.; Bumgarner, D. L., *J. Heterocycl. Chem.* **1981**, *18*, 417.
27. Chikashita, H.; Ishihara, M.; Takigawa, K.; Itoh, K., *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3256.
28. Kametani, T.; Suzuki, T.; Ogasawara, K., *Chem. Pharm. Bull.* **1972**, *20*, 2057.
29. Dondoni, A.; Marra, A.; Perrone, D., *J. Org. Chem.* **1993**, *58*, 275.
30. O'Connell, J. F.; Rapoport, H., *J. Org. Chem.* **1992**, *57*, 4775.
31. Vedejs, E.; Grissom, J. W., *J. Am. Chem. Soc.* **1988**, *110*, 3238.
32. Bosch, J.; Rubiralta, M.; Moral, M.; Valls, M., *J. Heterocycl. Chem.* **1983**, *20*, 595.
33. Hershenson, F. M.; Pavia, M. R., *Synthesis* **1988**, 999.
34. Knaus, E. E.; Ondrus, T. A.; Giam, C. S., *J. Heterocycl. Chem.* **1976**, *13*, 789.
35. Booth, B. L.; Jibodu, K. O.; Proenca, M. F. J. R. P., *J. Chem. Soc., Chem. Commun.* **1980**, 1151.
36. Borch, R. F., *J. Chem. soc., Chem. Commun.* **1968**, 442.
37. Fry, J. L.; Ott, R. A., *J. Org. Chem.* **1981**, *46*, 602.
38. Booth, B. L.; Jibodu, K. O.; Proenca, M. F. J. R. P., *J. Chem. Soc., Perkin Trans. 1* **1983**, 1067.
39. Amer, M. I. K.; Booth, B. L., *J. Chem. Res. (S)* **1993**, 4.
40. Carboni, B.; Carrie, R., *Tetrahedron* **1984**, *40*, 4115.
41. Quast, H.; Hergenroether, T., *Liebigs Ann. Chem.* **1992**, 581 (*Chem. Abstr.* **1992**, *117*, 48 426e).
42. King, J. F.; du Manior, J. R., *J. Am. Chem. Soc.* **1975**, *97*, 2566.
43. King, J. F.; Lee, T. M., *J. Chem. Soc., Chem. Commun.* **1978**, 48.
44. King, J. F.; Lee, T. M. L., *Can. J. Chem.* **1981**, *59*, 356.
45. Ferguson, A. N., *Tetrahedron Lett.* **1973**, 2889.
46. Milliet, P.; Picot, A.; Lusinchi, X., *Tetrahedron Lett.* **1976**, 1573, 1577.
47. Penczek, S.; Kubisa, P., In *Ring Opening Polymerization*; Brunelle, D. J., Ed.; Hanser, 1993; Chapter 2.
48. Pelter, A.; Colclough, M. E., *Tetrahedron Lett.* **1986**, *27*, 1935.
49. Quirk, R. P.; Gambill, C. R.; Thyvelikakath, G. X., *J. Org. Chem.* **1981**, *46*, 3181.
50. Tsay, S. C.; Robl, J. A.; Hwu, J. R., *J. Chem. Soc., Perkin Trans. 1* **1990**, 757.
51. Kreher, R. P.; Hennige, H.; Konrad, M.; Uhrig, J.; Clemens, A., *Z. Naturforsch., Teil B* **1991**, *46*, 809 (*Chem. Abstr.* **1991**, *115*, 92 001v) and references therein.

52. Arnarp, J.; Kenne, L.; Lindbreg, B.; Lönngren, J., *Carbohydr. Res.* **1975**, *44*, C5; Arnarp, J.; Lönngren, J., *Acta Chem. Scand.* **1978**, *32B*, 465. Berry, J. M.; Hall, L. D. J., *Carbohydr. Res.* **1976**, *47*, 307. Gilleron, M.; Fournie, J. J.; Pougny, J. R.; Puzo, G., *J. Carbohydr. Chem.* **1988**, *7*, 733.
53. Prehm, P., *Carbohydr. Res.* **1980**, *78*, 372.
54. Evans, D. A.; Sheppard, G. S., *J. Org. Chem.* **1990**, *55*, 5192.
55. Goldman, H. D.; Hsu, F. F.; Sherman, W. R., *Biomed. Environ. Mass Spectrom.* **1990**, *19*, 771.
56. Schmidt, R. R.; Moering, U.; Reichrath, M., *Chem. Ber.* **1982**, *115*, 39 (*Chem. Abstr.* **1982**, *96*, 123 134m).
57. Drozd, V. N.; Grandberg, N. V.; Udachin, Y. M., *Zh. Org. Khim.* **1982**, *18*, 1249 (*Chem. Abstr.* **1982**, *97*, 109 904b).
58. Roberts, R. M. G.; Tillett, J. G.; Ravenscroft, M., *J. Chem. Soc., Perkin Trans. 2* **1982**, 1569.
59. Okuma, K.; Koike, T.; Yamamoto, S.; Yonekura, K.; Ohta, H., *Chem. Lett.* **1989**, 1953.
60. Frasch, M.; Mono, S.; Pritzkow, H.; Sundermeyer, W., *Chem. Ber.* **1993**, *126*, 273.
61. Minato, H.; Okuma, K.; Kobayashi, M., *J. Org. Chem.* **1978**, *43*, 652 and references therein.
62. Durst, H. D.; Zubrick, J. W.; Kieczyowski G. R., *Tetrahedron Lett.* **1974**, 1777.
63. Brillon, D., *Synth. Commun.* **1990**, *20*, 3085.
64. Barton, D. H. R.; Hesse, R. H.; O'Sullivan, A. C.; Pechet, M. M., *J. Org. Chem.* **1991**, *56*, 6697.
65. Fetizon, M.; Jurion, M., *J. Chem. Soc., Chem. Commun.* **1972**, 382.
66. Ho, T. L.; Wong, C. M., *Synthesis* **1972**, 561.
67. Marshall, J. A.; Seitz, D. E., *J. Org. Chem.* **1975**, *40*, 534.
68. Corey, E. J.; Hase, T., *Tetrahedron Lett.* **1975**, 3267.
69. Hase, T. A.; Kivikari, R., *Synth. Commun.* **1979**, *9*, 107.
70. Lonn, H., *Carbohydr. Res.* **1985**, *139*, 105, 115.
71. Liptak, A.; Szabo, L., *Carbohydr. Res.* **1988**, *184*, C5.
72. Halazy, S.; Krief, A., *Tetrahedron Lett.* **1979**, 4233.
73. Szele, I.; Kubisen, S. J.; Westheimer, F. H., *J. Am. Chem. Soc.* **1976**, *98*, 3533.
74. (a) Colle, K. S.; Lewis, E. S., *J. Org. Chem.* **1978**, *43*, 571; (b) Lewis, E. S.; Hamp, D., *J. Org. Chem.* **1983**, *48*, 2025.
75. Omelanczuk, J.; Mikolajczyk, M., *Tetrahedron Lett.* **1984**, *25*, 2493.
76. Ahmed, M. G.; Alder, R. W., *J. Chem. Soc., Chem. Commun.* **1969**, 1389.
77. Beak, P.; Lee, J.; McKinnie, B. G., *J. Org. Chem.* **1978**, *43*, 1367.
78. Julia, S.; Ryan, R. J., *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *274*, 1207 (*Chem. Abstr.* **1972**, *77*, 5657u).
79. Press, J. B.; Shechter, H., *Tetrahedron Lett.* **1972**, 2677.
80. Foster, S. J.; Rees, C. W.; Williams, D. J., *J. Chem. Soc., Perkin Trans. 1* **1985**, 711 and references therein.
81. O'Neill, P.; Hegarty, A. F., *J. Org. Chem.* **1987**, *52*, 2113.
82. Maruoka, K.; Sato, J.; Yamamoto, H., *J. Am. Chem. Soc.* **1992**, *114*, 4422.
83. Beaudoin, S.; Kinsey, K. E.; Burns, J. F., *J. Org. Chem.* **2003**, *68*, 115.
84. Yamamoto, Y.; Yamamoto, H., *J. Am. Chem. Soc.* **2004**, *126*, 4128.
85. Iradier, F.; Gomez-Arrayas, R.; Carretero, J. C., *Org. Lett.* **2001**, *3*, 2957.
86. Armstrong, A.; Draffan, A. G., *Synlett* **1998**, 646.
87. Gustafsson, M.; Olsson, R.; Andersson, C.-M., *Tetrahedron Lett.* **2002**, *42*, 133.
88. Blaney, P.; Grigg, R.; Rankovic, Z.; Thoroughgood, M., *Tetrahedron Lett.* **2000**, *41*, 6639.
89. Degnan, A. P.; Meyers, A. I., *J. Org. Chem.* **2000**, *65*, 3503.
90. Florio, S.; Capriati, V.; Di Martino, S.; Abbotto, A., *Eur. J. Org. Chem.* **1999**, 409.
91. Wenkert, D.; Chen, T.-F.; Ramachandran, K.; Valasinas, L.; Weng, L. I.; McPhail, A. T., *Org. Lett.* **2001**, *3*, 2301.
92. Miyamoto, M.; Aoi, K.; Saegusa, T., *J. Polym. Sci. Part A: Polym. Chem.* **1997**, *35*, 933.
93. Någren, K.; Sutinen, E.; Jyrkkiö, S., *J. Label. Compd. Radiopharm.* **2000**, *43*, 1013.
94. Kozmin, S. A., *Org. Lett.* **2001**, *3*, 755.
95. Christoph, G.; Hoppe, D., *Org. Lett.* **2002**, *4*, 2189.
96. Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M., *J. Am. Chem. Soc.* **2001**, *123*, 10942.
97. Gotoh, Y.; Saitoh, H.; Miyake, T., *Carbohydr. Res.* **1998**, *309*, 45.
98. Sparks, S. M.; Shea, K. J., *Org. Lett.* **2001**, *3*, 2265.
99. Baxter, E. W.; Labaree, D.; Ammon, H. L.; Mariano, P. S., *J. Am. Chem. Soc.* **1990**, *112*, 7682.
100. Kolomeitsev, A. A.; Kadyrov, A. A.; Szczepkowska-Sztolcman, J.; Milewska, M.; Koroniak, H.; Bissky, G.; Barten, J. A.; Röschenthaler, G.-V., *Tetrahedron Lett.* **2003**, *44*, 8273.
101. Barluenga, J.; Dieguez, A.; Rodriguez, F.; Florez, J.; Fananas, F. J., *J. Am. Chem. Soc.* **2002**, *124*, 9056.
102. Kanoh, S.; Nishimura, T.; Kita, Y.; Ogawa, H.; Motoi, M.; Takani, M.; Tanaka, T., *J. Org. Chem.* **2000**, *65*, 2253.
103. Brenneman, J. B.; Martin, S. F., *Org. Lett.* **2004**, *6*, 1329.
104. Bates, R. B.; Taylor, S. R., *J. Org. Chem.* **1993**, *58*, 4469.
105. Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J., *Org. Lett.* **1999**, *1*, 87.
106. Smith, T. E.; Mourad, M. S.; Velander, A. J., *Heterocycles* **2002**, *57*, 1211.
107. Nakamura, S.; Furutani, A.; Toru, T., *Eur. J. Org. Chem.* **2002**: 1690.
108. Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P., *J. Am. Chem. Soc.* **2001**, *124*, 11689.
109. Larsen, S. D.; DiPaolo, B. A., *Org. Lett.* **2001**, *3*, 3341.
110. Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M., *J. Am. Chem. Soc.* **2004**, *126*, 5968.
111. Murai, T.; Mutoh, Y.; Kato, S., *Org. Lett.* **2001**, *3*, 1993.
112. Schiavi, B. M.; Richard, D. J.; Joullie, M. M., *J. Org. Chem.* **2002**, *67*, 620.
113. Morita, M.; Inoue, K.; Ogoshi, S.; Kurosawa, H., *Organometallics* **2003**, *22*, 5468.
114. Djukic, J.- P.; Michon, C.; Maisse-François, A.; Allagapen, R.; Pfeffer, M.; Dötz K. H.; De Cian, A.; Fischer, J., *Chem. Eur. J.* **2000**, *6*, 1064.
115. Djukic, J.-P.; Maisse-Francois, A.; Pfeffer, M.; Dötz K. H.; De Cian, A.; Fischer, J., *Organometallics* **2000**, *19*, 5484.
116. Hevia, E.; Perez, J.; Riera, V.; Miguel, D.; Campomanes, P.; Menendez, M. I.; Sordo, T. L.; Garcia-Granda, S., *J. Am. Chem. Soc.* **2003**, *125*, 3706.
117. Nückel, S.; Burger, P., *Organometallics* **2001**, *20*, 4345.
118. Dieckbreder, U.; Röschenthaler, G.-V.; Kolomeitsev, A. A., *Heteroatom Chem.* **2002**, *13*, 650.
119. Merceron-Saffon, N.; Baceiredo, A.; Gornitzka, H.; Bertrand, G., *Science* **2003**, *301*, 1223.
120. Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y., *Org. Lett.* **2001**, *3*, 87.
121. Lönn, H., *Carbohydr. Res.* **1987**, *139*, 105.
122. Hansson, J.; Garegg, P. J.; Oscarson, S., *J. Org. Chem.* **2001**, *66*, 6234.
123. Takatani, M.; Nakano, J.; Arai, M. A.; Ishiwata, A.; Ohta, H.; Ito, Y., *Tetrahedron Lett.* **2004**, *45*, 3929.
124. Nilsson, S.; Lönn, H.; Norberg, T., *Glycocojugate J.* **1991**, *8*, 9.
125. Matsuo, I.; Wada, M.; Manabe, S.; Yamaguchi, Y.; Otake, K.; Kato, K.; Ito, Y., *J. Am. Chem. Soc.* **2003**, *125*, 3402.

126. Yang, Z.; Cao, H.; Hu, J.; Shan, R.; Yu, B., *Tetrahedron* **2003**, *59*, 249.
127. Ziegler, T.; Lemanski, G., *Angew. Chem. Int. Ed.* **1998**, *37*, 3129.
128. Demchenko, A. V.; De Meo, C., *Tetrahedron Lett.* **2002**, *43*, 8819.
129. Hanessian, S.; Lou, B., *Chem. Rev.* **2000**, *100*, 4443.
130. Demchenko, A. V.; Malysheva, N. N.; De Meo, C., *Org. Lett.* **2003**, *5*, 455.

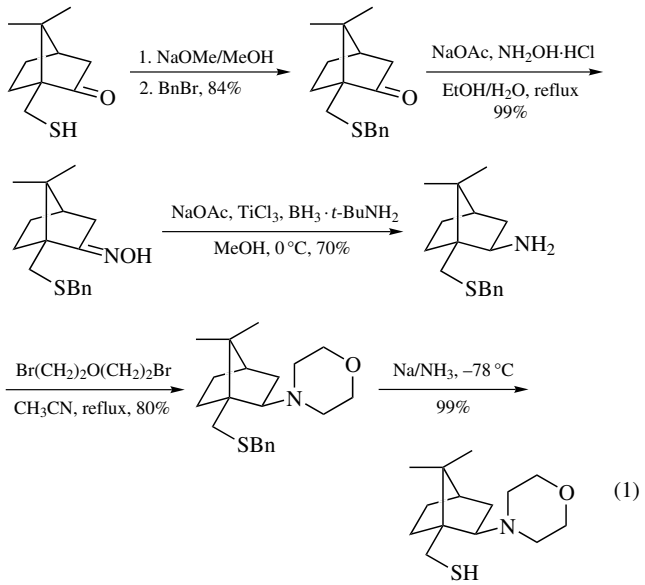
(–)-2-*exo*-Morpholinoisobornane-10-thiol



[874896-16-9] $C_{14}H_{25}NOS$ (MW 255.42)
InChI = 1/C14H25NOS/c1-13(2)11-3-4-14(13,10-17)12(9-11)15-5-7-16-8-6-15/h11-12,17H,3-10H2,1-2H3
InChIKey = RXWAXIDATPTAOS-UHFFFAOYAQ

(a chiral ligand for catalytic asymmetric addition of Et_2Zn, alkenylzinc, and arylzinc reagents to aldehydes)

Alternate Name: MITH.
Physical Data: viscous oil, bp 90–92 °C (0.4 mmHg), $[\alpha]_D^{24}$ −79.8 (*c* 0.9, $CHCl_3$).
Solubility: soluble in hexane, pentane, toluene, and other common organic solvents.
Form Supplied in: not commercially available.
Analysis of Reagent Purity: ^1H and ^{13}C NMR.
Preparative Methods: it can be synthesized from 10-mercaptobornane-2-one[1] in five synthetic steps (eq 1).

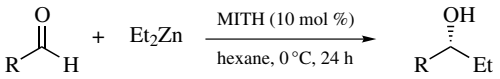


(1)

Purification: can be purified by column chromatography on SiO_2 (ethyl acetate/hexane 1:20).
Handling, Storage, and Precautions: storage of MITH under inert atmosphere in the refrigerator is recommended to prevent oxidation of the primary thiol functional group.

Since the discovery of Et_2Zn, the syntheses of organozinc reagents and their utilization and applications in the construction of C–C bonds have received tremendous attention. Particularly, the catalytic asymmetric additions of organozinc reagents to aldehydes have been widely studied. MITH, a camphor-based γ-amino thiol ligand, was developed for the studies of asymmetric addition of organozinc reagents to carbonyl compounds. In the presence of MITH, additions of Et_2Zn, alkenylzinc, and arylzinc reagents to aldehydes afford the corresponding optically active alcohols in excellent yields and enantioselectivities.

Catalytic Asymmetric Addition of Et_2Zn to Aldehydes. In the presence of 10 mol % of MITH, the addition of Et_2Zn to aldehydes gave the corresponding chiral alcohols with excellent enantioselectivities and yields (eq 2) (Table 1).[2] The asymmetric addition of Et_2Zn to substituted benzaldehydes, bearing either electron-withdrawing or electron-donating groups, provided ethylated alcohols with 96–98% ee together with 85–95% yield. A positive nonlinear effect[3–5] was observed in the case of the Et_2Zn addition reaction (Figure 1)



(2)

70–95% yield
95–98% ee

Table 1 Catalytic asymmetric addition of Et_2Zn to aldehydes using MITH as a ligand

Entry	R	Yield (%)	ee (%)
1	C_6H_5	92	98
2	2-Cl-C_6H_4	89	98
3	3-Cl-C_6H_4	90	96
4	2-Me-C_6H_4	88	96
5	3-Me-C_6H_4	91	96
6	4-Me-C_6H_4	95	96
7	4-^{t}Bu-C_6H_4	91	97
8	3-MeO-C_6H_4	92	97
9	4-MeO-C_6H_4	92	96
10	1-Naph	85	96
11	3-CF_3-C_6H_4	88	98
12	4-CF_3-C_6H_4	85	96
13	Cyclohexyl	70	97
14	2-Me-cinnamyl	90	95

Catalytic Asymmetric Addition of Alkenylzinc Reagents to Aldehydes. The catalytic asymmetric addition of alkenylzinc reagents[6] to aldehydes catalyzed by MITH produced the corresponding (*E*)-allylic alcohols with >95% ee (eq 3) (Table 2).[7] In the case of 4-trifluorobenzaldehyde, the reaction afforded the adduct with >99.5% ee. It should be noted that MITH is an effective and efficient ligand to catalyze the addition of disubstituted (R_2= R_3= ethyl) (Table 2, entry 13) and bulky substituted (R_2 = H, R_3 = *tert*-butyl) (entry 14) alkenylzinc reagents to benzaldehyde, generating the corresponding allylic alcohols both with 96% ee.[8–12] This methodology features a regioselective synthesis of an (*E*)-double bond and an asymmetric C–C bond formation with excellent enantioselectivity, and the chiral allylic alcohols thus obtained are important and useful precursors for the syntheses of natural

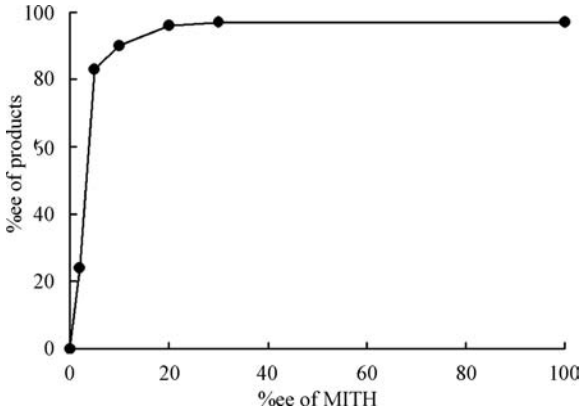
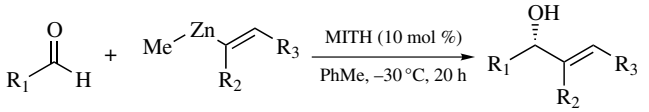


Figure 1 Nonlinear effect in the asymmetric addition of Et_2Zn to benzaldehydes catalyzed by MITH

products and biologically active componds.[9,13–16]

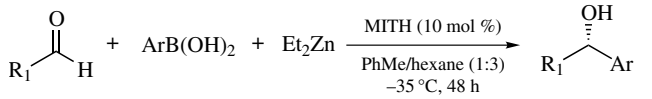


75–91% yield
95 to >99.5% ee
(3)

Table 2 Catalytic asymmetric alkenylation of various aldehydes

Entry	R_1	R_2	R_3	Yield (%)	ee(%)
1	C_6H_5	H	C_6H_{13}	85	96
2	2-Cl-C_6H_4	H	C_6H_{13}	85	95
3	3-Cl-C_6H_4	H	C_6H_{13}	88	97
4	4-Cl-C_6H_4	H	C_6H_{13}	90	96
5	3-F-C_6H_4	H	C_6H_{13}	88	96
6	2-Me-C_6H_4	H	C_6H_{13}	83	96
7	4-Me-C_6H_4	H	C_6H_{13}	83	95
8	3-MeO-C_6H_4	H	C_6H_{13}	81	95
9	3-CF_3-C_6H_4	H	C_6H_{13}	87	98
10	4-CF_3-C_6H_4	H	C_6H_{13}	90	>99.5
11	C_6H_5	H	C_4H_9	83	97
12	3-CF_3-C_6H_4	H	C_4H_9	82	98
13	C_6H_5	C_2H_5	C_2H_5	89	96
14	C_6H_5	H	^{t}Bu	91	96
15	Cyclohexyl	H	$Ph(CH_2)_3$	80	97

Catalytic Asymmetric Addition of Arylzinc Reagents to Aldehydes. The catalytic asymmetric addition of arylzinc reagents, which were prepared in situ from reaction of arylboronic acid[17] and Et_2Zn, to aromatic aldehydes afforded the corresponding diarylmethanols with 95 to >99.5% ee and 73–98% yield (eq 4) (Table 3).[18] Additionally, two aliphatic aldehydes such as cyclohexanecarboxaldehyde and pivalaldehyde were also examined as substrates and their corresponding adducts were obtained with 98 and 93% ee, respectively. Notably, the asymmetric arylation of the phenylzinc reagent with 2-tolylaldehyde provided (*R*)-phenyl-*o*-tolylmethanol,[19] a direct precursor to synthesize the anticholinergic and antihistamine agent (*R*)-orphenadrine, with 95% yield and >99.5% ee. This method features the asymmetric addition of an arylzinc to aldehydes that could be achieved with excellent enantioselectivities without other additive.



73–98% yield
95 to >99.5% ee
(4)

Table 3 Catalytic asymmetric arylation of various aldehydes

Entry	R_1	Ar	Yield (%)	ee (%)
1	2-Me-C_6H_4	C_6H_5	89	>99.5
2	3-Me-C_6H_4	C_6H_5	90	97
3	4-Me-C_6H_4	C_6H_5	84	97
4	2-Cl-C_6H_4	C_6H_5	90	98
5	3-Cl-C_6H_4	C_6H_5	96	95
6	4-Cl-C_6H_4	C_6H_5	96	96
7	4-MeO-C_6H_4	C_6H_5	73	97
8	4-CF_3-C_6H_4	C_6H_5	83	97
9	4-CO_2Me-C_6H_4	C_6H_5	84	96
10	2-Naph	C_6H_5	73	95
11	Cyclohexyl	C_6H_5	78	98
12	^{t}Bu	C_6H_5	32	93
13	C_6H_5	4-Me-C_6H_4	86	97
14	C_6H_5	4-Cl-C_6H_4	98	96

1. Oae, S.; Yogo, S., *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3802.
2. Wu, H. L., Ph. D. dissertation, National Tsing Hua University, Hsinchu, Taiwan, 2004.
3. Oguni, N.; Matsuda, Y.; Kaneko, T., *J. Am. Chem. Soc.* **1988**, *110*, 7877.
4. Kitamura, M.; Okada, S.; Suga, S.; Noyori, R., *J. Am. Chem. Soc.* **1989**, *111*, 4028.
5. Girard, C.; Kagan, H. B., *Angew. Chem., Int. Ed.* **1998**, *37*, 2922.
6. Oppolzer, W.; Radinov, R. N., *Helv. Chim. Acta* **1992**, *75*, 170.
7. Wu, H. L.; Wu, P. Y.; Uang, B. J., *J. Org. Chem.* **2007**, *72*, 5935.
8. Wipf, P.; Ribe, S., *J. Org. Chem.* **1998**, *63*, 6454.
9. Chen, Y. K.; Lurain, A. E.; Walsh, P. J., *J. Am. Chem. Soc.* **2002**, *124*, 12225.
10. Bräse, S.; Dahmen, S.; Höfener, S.; Lauterwasser, F.; Kreis, M.; Ziegert, R. E., *Synlett* **2004**, 2647.
11. Sprout, C. M.; Richmond, M. L.; Seto, C. T., *J. Org. Chem.* **2005**, *70*, 7408.
12. Richmond, M. L.; Sprout, C. M.; Seto, C. T., *J. Org. Chem.* **2005**, *70*, 8835.
13. Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J., *J. Am. Chem. Soc.* **2004**, *126*, 13608.
14. Lurain, A. E.; Carroll, P. J.; Walsh, P. J., *J. Org. Chem.* **2005**, *70*, 1262.
15. Jeon, S. J.; Chen, Y. K.; Walsh, P. J., *Org. Lett.* **2005**, *7*, 1729.
16. Kelly, A. R.; Lurain, A. E.; Walsh, P. J., *J. Am. Chem. Soc.* **2005**, *127*, 14668.
17. Bolm, C.; Rudolph, J., *J. Am. Chem. Soc.* **2002**, *124*, 14850.
18. Wu, P. Y.; Wu, H. L.; Uang, B. J., *J. Org. Chem.* **2006**, *71*, 833.
19. Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C., *Chem. Soc. Rev.* **2006**, *35*, 454.

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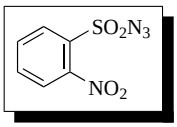
o-Nitrobenzenesulfonyl Azide



[6655-31-8] $C_6H_4N_4O_4S$ (MW 228.21)

InChI = 1/C6H4N4O4S/c7-8-9-15(13,14)6-4-2-1-3-5(6)10(11)12/h1-4H
InChIKey = MNMURNLWLUKMSZ-UHFFFAOYAN

(1,3-dipolar reagent that undergoes cycloaddition to alkenes, enamines, enol ethers, and enynes[1])

Physical Data: mp 71–73 °C.

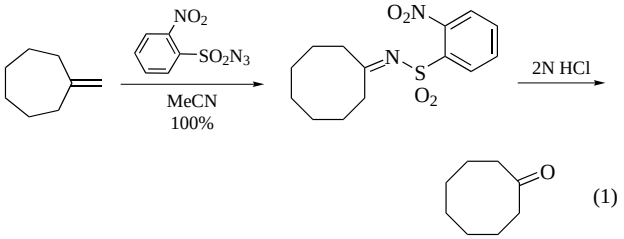
Solubility: sol most organic solvents.

Preparative Method: by the reaction of *o*-nitrobenzenesulfonyl chloride with an aqueous acetone solution of sodium azide, first at 0 °C and then at 25 °C.[2]

Purification: crystallization from ethanol.[2]

Handling, Storage, and Precautions: azides should be expected to be sensitive to electrical, thermal, and/or mechanical shock. The parent sulfonyl azide, benzenesulfonyl azide, in the crude state, detonates violently when heated.

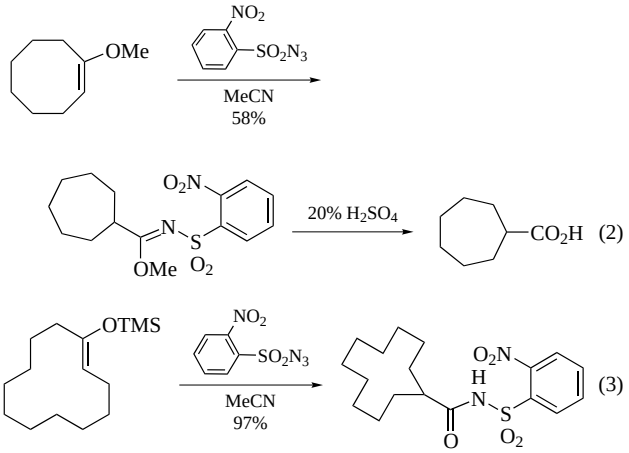
Dipolar Cycloaddition. *o*-Nitrobenzenesulfonyl azide has been used for the ring enlargement–conversion of methylenecycloalkanes into the homologous *o*-nitrobenzenesulfonimidocycloalkanes. For example, methylenecycloheptane affords the imido product in quantitative yield. Hydrolysis of the imide with acid then affords the corresponding ketone (eq 1).[3]

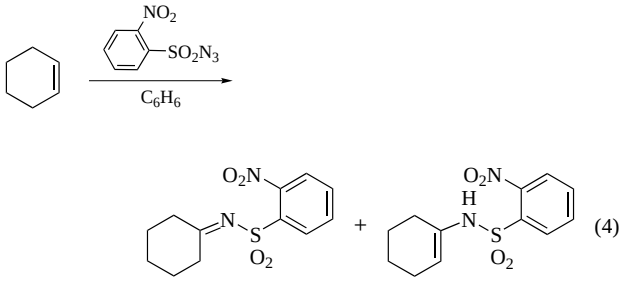


(1)

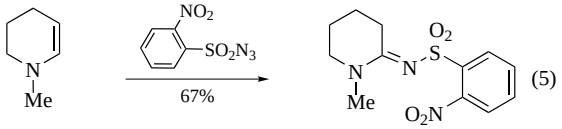
The reagent has also been employed for the cycloaddition–rearrangement of both methyl and trimethylsilyl enol ethers (eqs 2 and 3).[4,5]

Decomposition of the reagent in boiling benzene–cyclohexene affords a quantitative yield of a 3:1 mixture of imide and enesulfonamide (eq 4).[6]

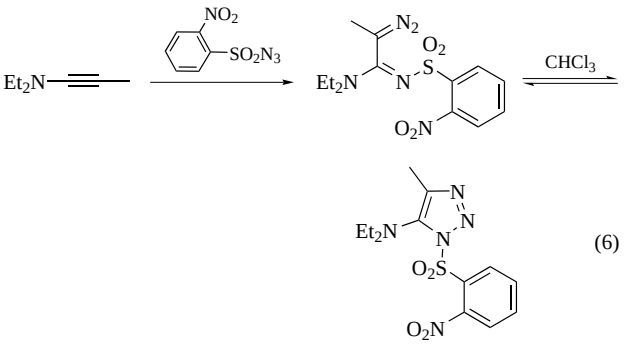




With a cyclic enamine, *o*-nitrobenzenesulfonyl azide affords an *N*-sulfonyl amidine following decomposition of an unstable intermediate triazoline (eq 5).[7]



The reaction of *o*-nitrobenzenesulfonyl azide with an ynamine leads to a 2-diazoalkanamidine as the only isolable product. An equilibrium between the amidine and the ring-closed triazole exists, however, in solution (eq 6).[8]



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1. *1,3-Dipolar Cycloaddition Chemistry*; Lwowski, W., Ed.; Wiley: New York, 1984; 1, p 817.
2. Leffler, J. E.; Tsuno, Y., *J. Org. Chem.* **1963**, *28*, 902.
3. Wohl, R., *J. Org. Chem.* **1973**, *38*, 3862.
4. Wohl, R. A., *Helv. Chim. Acta* **1973**, *56*, 1826.
5. Wohl, R. A., *Tetrahedron Lett.* **1973**, 3111.

6. Abramovitch, R. A.; Knaus, G. N.; Pavlin, M.; Holcomb, W. D., *J. Chem. Soc., Perkin Trans. 1* **1974**, 2169.
7. Warren, B. K.; Knaus, E. E., *J. Heterocycl. Chem.* **1987**, *24*, 1413.
8. Himbert, G.; Regitz, M., *Justus Liebigs Ann. Chem.* **1974**, 1505.

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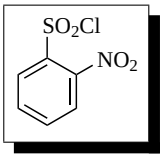
o-Nitrobenzenesulfonyl Chloride

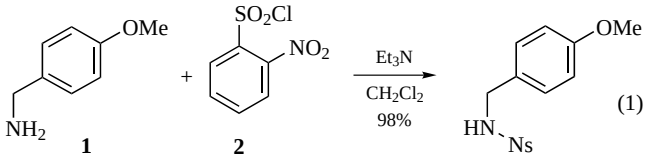


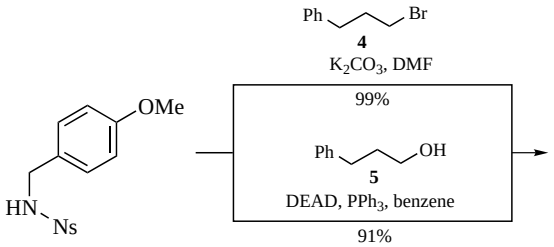
[1694-92-4] $C_6H_4NO_4ClS$ (MW 221.62)
InChI = 1/C6H4ClNO4S/c7-13(11,12)6-4-2-1-3-5(6)8(9)10/h1-4H
InChIKey = WPHUUIODWRNJLO-UHFFFAOYAG

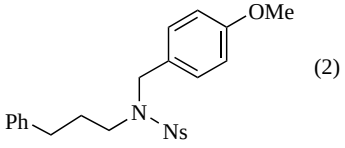
(reagent used in the protection of primary and secondary amines as their nitrobenzenesulfonamides; alkylation of the sulfonamides proceeds smoothly by conventional means or under Mitsunobu conditions; the nitrobenzenesulfonamide is removed easily with soft nucleophiles via Meisenheimer complexes to give the corresponding secondary amines)[1]

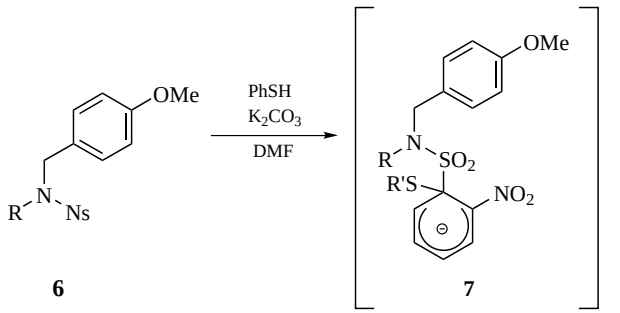
Alternate Name: nosyl chloride, NsCl.
Physical Data: mp 67–69 °C; pale yellow solid.
Solubility: soluble in most common organic solvents.
Form Supplied in: pale yellow crystals.
Handling, Storage, and Precaution: moisture sensitive; stable for one year under nitrogen and protected from light at 0 °C.

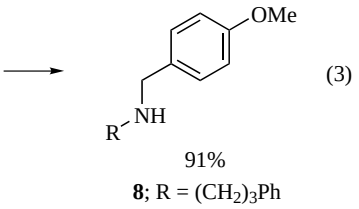
Secondary Amine Synthesis from Primary Amines.[2,3] Although sulfonamides are reliable protecting groups for amines as a result of their stability under various conditions, deprotection of sulfonamides usually requires relatively harsh conditions (for example, Ts or Ms groups). However, deprotection of the nitrobenzenesulfonyl group (Ns group) is carried out under mild conditions. In addition, its remarkable alkylating ability provides an efficient synthetic method for the preparation of nitrogen-containing compounds (Ns strategy). An example of the Ns strategy is described in eqs 1–3. Protection of primary amine **1** was carried out by treatment with NsCl (**2**) and a base (triethylamine, pyridine, or 2,6-lutidine) to give *N*-monosubstituted nitrobenzenesulfonamide (**3**) in high yield. Alkylation of **3** proceeded smoothly by either conventional alkylation with **4** or under Mitsunobu conditions with **5** to give the *N*,*N*-disubstituted sulfonamide (**6**) in excellent yields. Facile deprotection of the Ns group of **6** was achieved by treatment with the thiolate nucleophile, presumably via formation of the Meisenheimer complex (**7**), and gave the desired secondary amine **8**. In the deprotection step, one of the following reported procedures is recommended: (a) PhSH, Cs_2CO_3 in CH_3CN or (b) $HSCH_2CH_2OH$, DBU in DMF.





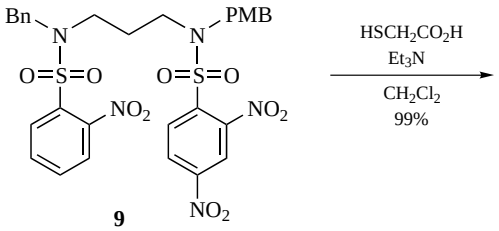






Since the Ns group is stable under acidic [HCl (10 equiv), MeOH, 60 °C, 4 h] as well as basic [NaOH (10 equiv), MeOH, 60 °C, 4 h] conditions, it can be used for protection of both primary and secondary amines.

Selective Deprotection of DNs Group.[4] 2,4-Dinitrobenzenesulfonamides (DNs) also can be easily alkylated, analogous to Ns amides. However, the particular advantage of the DNs group is that the deprotection proceeds under milder conditions than for the Ns group. Thus the selective removal of the DNs group in the presence of the Ns group was performed by treatment with $HSCH_2CO_2H$ and Et_3N to give desired amine **10** in nearly quantitative yields (eq 4).



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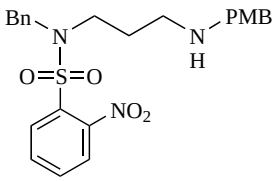
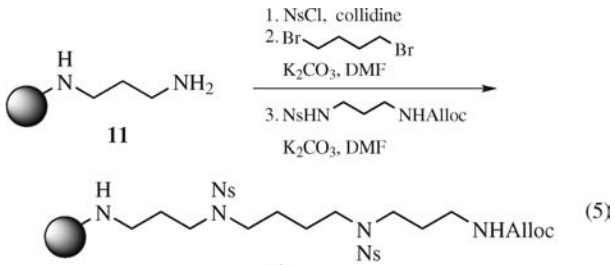


(4)

10

Solid-phase Synthesis.[5,6] The Ns strategy can be applied to solid-phase synthesis since the alkylation and deprotection steps proceed smoothly on the resin (eq 5). After attachment of the diamine to the trityl-type resin, protection of the less-hindered amine of **11** was carried out by treatment with NsCl and collidine. Elongation of the polyamine chain was performed by stepwise alkylation with dibromobutane and Ns amide to give the protected spermine derivative **12**.

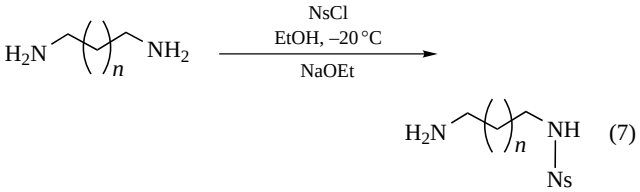


(5)

11 **12**

As shown in (eq 6), the deprotection of the Ns group of **13**, bound to the resin, was effected by treatment with 2-mercaptoethanol and DBU. Final cleavage from the resin was performed under acidic conditions (1% TFA/CH_2Cl_2). Upon removal of the solvent, PhTX-343 (**14**) was obtained in high purity without any purification.

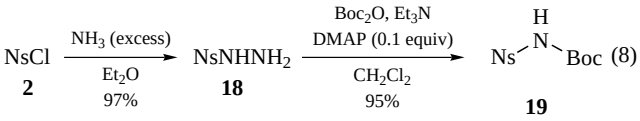
Mono-nosylation of Diamines.[7,8] Selective monoprotection of the symmetrical diamines was performed by treatment with NsCl in EtOH (eq 7). After neutralization with NaOEt, mononosylated diamine **15** was obtained in high yield. This procedure has been applied to other diamines to provide **16** and **17** in high yield. These diamine derivatives are ideal starting materials for natural polyamines.



(7)

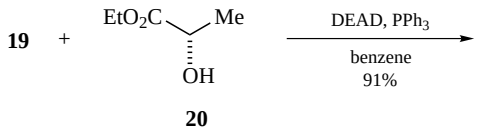
15; n = 1 (83% from NsCl)
16; n = 2 (77% from NsCl)
17; n = 3 (87% from NsCl)

Synthesis of Protected Primary Amines.[9] Ns amide (**18**) and its Boc derivative **19** readily obtained from **2** are valuable nitrogen nucleophiles for the preparation of *N*-protected primary amines from the corresponding alcohol and halide (eq 8). A representative example of the Mitsunobu reaction of NsNHBoc (**19**) and (−)-ethyl lactate (**20**) is described in (eq 9). Both the Ns and the Boc groups of alkyl sulfonamide **21** can be selectively deprotected without affecting the other functional groups (eq 10). After deprotection of the Ns group of **21**, the *N*-Boc amines (**22**) can be converted into primary amines. Alternatively, treatment of **21** with excess trifluoroacetic acid afforded the *N*-monoalkylated sulfonamides (**23**), which in turn could serve as the precursor for secondary amines (eq 11). Furthermore, the Cbz and Alloc derivatives of **19** can also be readily prepared from **18**.



(8)

2 **18** **19**



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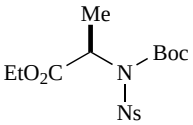

(9)

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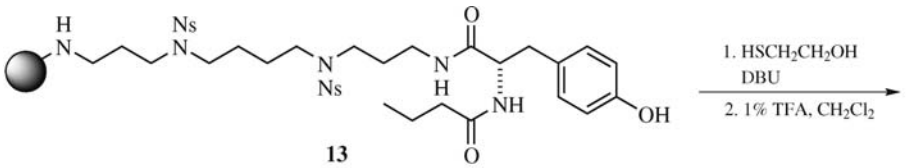
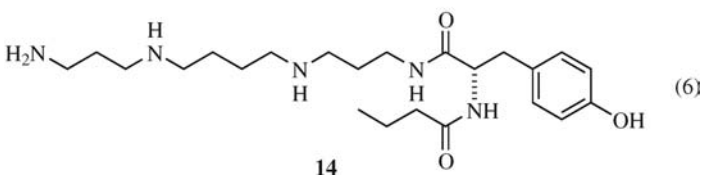


13



(6)

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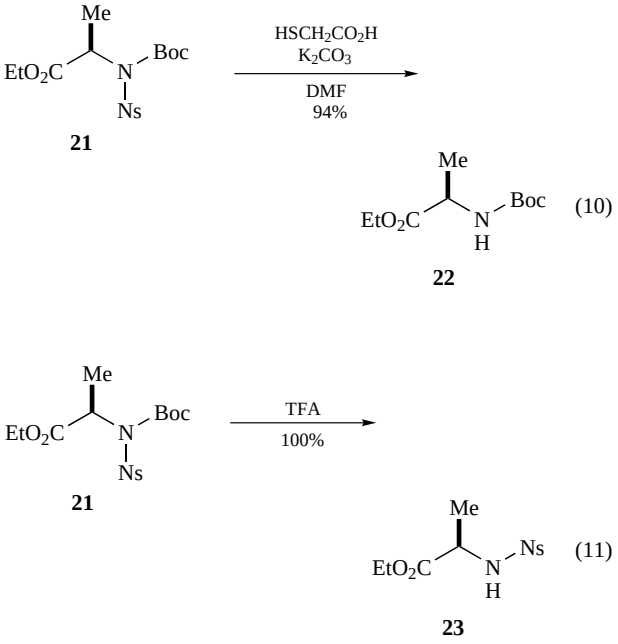
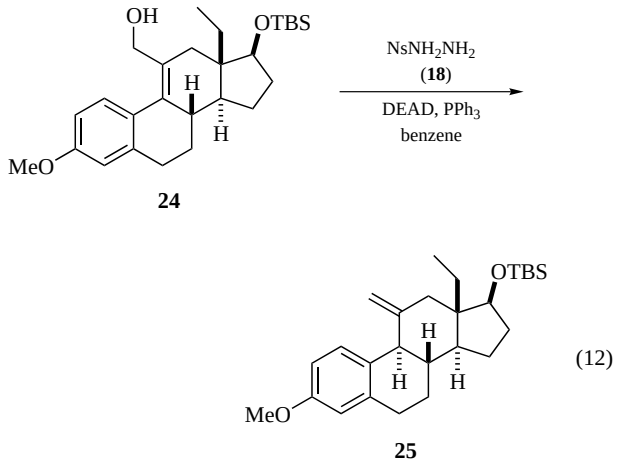
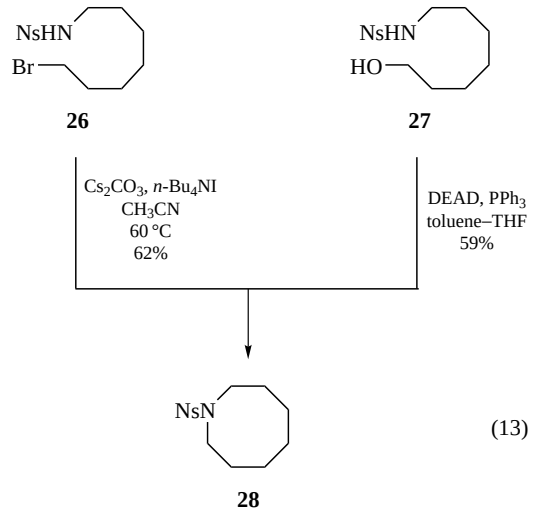


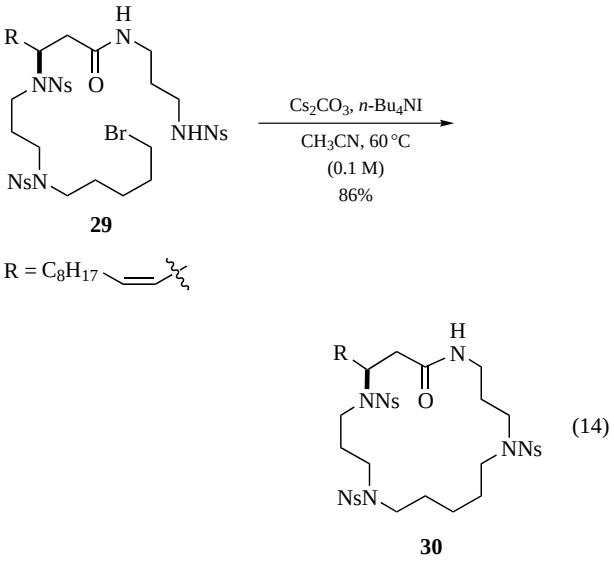
Reductive Deoxygenation of Allylic Alcohol/Allylic Diazene Rearrangement.[10,11] Upon condensation of allylic alcohol **24** and $NsNHNH_2$ (**18**) under Mitsunobu conditions, the smooth reductive deoxygenation reaction proceeded stereoselectively to give **25** (eq 12). This reaction could be explained by a [3,3]-sigmatropic rearrangement of the allylic diazene intermediate after alkylation of the sulfonamide and elimination of the sulfonic acid. Furthermore, this protocol can be applicable for the preparation of allene derivatives from the corresponding propargyl alcohols.[12]



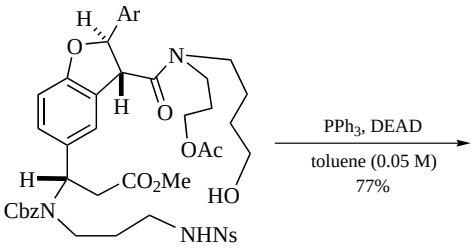
Construction of Medium-sized Rings.[13,14] Intramolecular alkylation of Ns amides provides an efficient synthetic protocol for medium-sized cyclic amines (eight- to ten-membered rings). As shown in (eq 13), the ring closure reactions of **26** and **27** proceed smoothly under conventional alkylation or Mitsunobu conditions to give eight-membered ring **28**. This protocol was also applicable for construction of nine- and ten-membered rings even with non-branched substrates.



Macrocyclization for Natural Product Synthesis.[15,16] Construction of large-sized rings was also readily performed by alkylation of the Ns group. The mild alkylation and deprotection conditions of the Ns strategy allow for the efficient total synthesis of natural products containing many functional groups. In the total synthesis of lipogrammistin-A, the efficient construction of the eighteen-membered ring was achieved by treatment of **29** with Cs_2CO_3 and tetrabutylammonium iodide to give **30** in high yield (eq 14). The ring closures were successfully performed even at 0.1 M concentrations, obviating the need for high-dilution conditions.



Construction of the macrocyclic ring of ephedradine-A was carried out under Mitsunobu conditions (eq 15). Upon treatment of **31** with DEAD and PPh_3 in 0.05 M toluene solution at room temperature, the desired cyclization proceeded smoothly to afford **32** in 77% yield. Since ephedradine-A possessed the acid- and/or base-labile dihydrobenzofuran and β-amino ester moieties, the synthetic utility of the Ns strategy for secondary amines was also demonstrated by this total synthesis.



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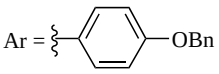

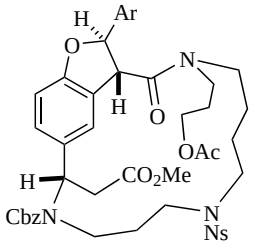

(15)

32

Related Reagents. 4-Nitrobenzenesulfonyl Chloride; 2,4-Dinitrobenzenesulfonyl Chloride; 2-Nitrobenzenesulfonamide.

1. (a) Kan, T.; Fukuyama, T., *J. Syn. Org. Chem. Jpn.* **2001**, *59*, 779. (b) *Chem. Commun.* **2004**, 353.
2. Kurosawa, W.; Kan, T.; Fukuyama, T., *Org. Synth.* **2002**, *79*, 186.
3. Fukuyama, T.; Jow, C.-K.; Cheung, M., *Tetrahedron Lett.* **1995**, *36*, 6373.
4. Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T., *Tetrahedron Lett.* **1997**, *38*, 5831.
5. Bennet, W. D., In *Combinatorial Chemistry: A Practical Approach*; Fenniri, H., Ed.; Oxford University Press: Oxford, p 139.
6. Kan, T.; Kobayashi, H.; Fukuyama, T., *Synlett* **2002**, 1338.
7. Hidai, Y.; Kan, T.; Fukuyama, T., *Tetrahedron Lett.* **1999**, *40*, 4711.
8. Hidai, Y.; Kan, T.; Fukuyama, T., *Chem. Pharm. Bull.* **2000**, *48*, 1570.
9. Fukuyama, T.; Cheung, M.; Kan, T., *Synlett* **1999**, 1301.
10. Myers, A. G.; Movassaghi, M.; Zheng, B., *J. Am. Chem. Soc.* **1997**, *119*, 8572.
11. Corey, E. J.; Huang, A. X., *J. Am. Chem. Soc.* **1999**, *121*, 710.
12. Myers, A. G.; Zheng, B., *J. Am. Chem. Soc.* **1996**, *118*, 4492.
13. Kan, T.; Kobayashi, H.; Fukuyama, T., *Synlett* **2002**, 697.
14. Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T., *Tetrahedron* **2002**, *58*, 6267.
15. Fujiwara, A.; Kan, T.; Fukuyama, T., *Synlett* **2000**, 1667.
16. Kurosawa, W.; Kan, T.; Fukuyama, T., *J. Am. Chem. Soc.* **2003**, *125*, 8112.

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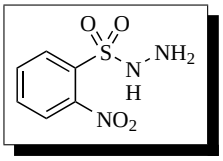
o-Nitrobenzenesulfonylhydrazide

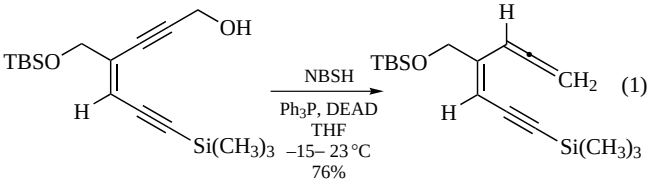


[5906-99-0] $C_6H_7N_3O_4S$ (MW 217.20)
InChI = 1/C6H7N3O4S/c7-8-14(12,13)6-4-2-1-3-5(6)9(10)11/h1-4,8H,7H2
InChIKey = QENBJCMCPIVGMF-UHFFFAOYAL

(reagent used for synthesis of allenes from propargylic alcohols, for the reductive transposition of allylic alcohols, for the deoxygenation of unhindered alcohols, and for the generation of diimide)

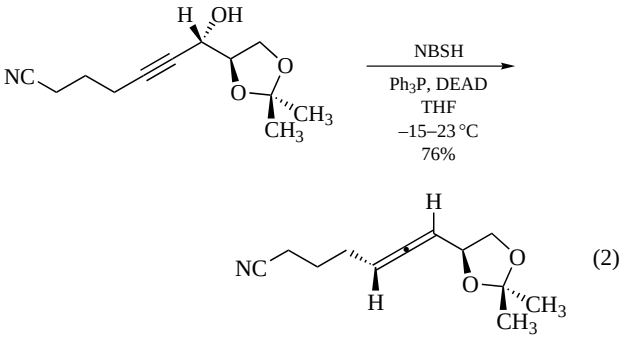
Alternate Name: NBSH.
Physical Data: mp 100–101 °C (dec).
Solubility: soluble in acetonitrile, ethyl acetate, *N*-methylmorpholine (NMM), THF, and water; insoluble in benzene and hexanes.
Form Supplied in: off-white solid.
Preparative Methods: prepared in one step from commercially available *o*-nitrobenzenesulfonyl chloride and hydrazine monohydrate in THF at −30 °C.[1]
Purity: a solution of NBSH in ethyl acetate is washed with ice-cold 10% aqueous sodium chloride, dried over anhydrous sodium sulfate, and diluted with hexanes at 23 °C to induce precipitation of NBSH.[1a]
Handling, Storage, and Precaution: stable at ambient temperature for several days, but should be refrigerated (−20 °C) for long-term storage.[1a]

Synthesis of Allenes.[2] The invertive Mitsunobu displacement of propargylic alcohols with *o*-nitrobenzenesulfonylhydrazide (NBSH)[1] occurs within 1–2 h at −15 °C in THF to afford the corresponding *N*,*N*-1-alkyl-1-*o*-nitrobenzenesulfonylhydrazine derivatives. Warming of the reaction mixture to ambient temperature leads to elimination of *o*-nitrobenzenesulfinic acid to give propargylic diazene intermediates that undergo spontaneous sigmatropic loss of dinitrogen to provide the corresponding allenes.[2a] The mild reaction conditions are compatible with a wide variety of functional groups and allow the synthesis of sensitive allene-ene-yne systems (eq 1).[2a] Valuable (trialkylsilyl)allenes, including (trimethylsilyl)allene and (*t*-butyldimethylsilyl)allene, are prepared in a single step from the corresponding *C*-silylated propargylic alcohol derivatives.[2b]



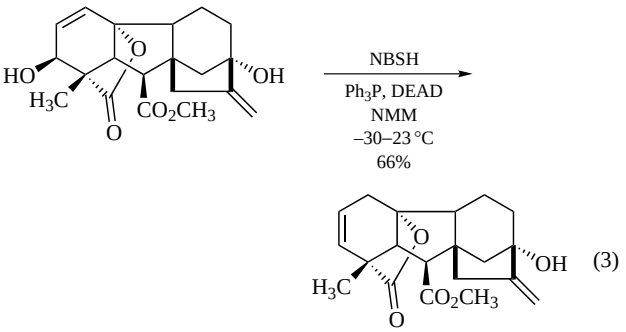
(1)

The overall transformation proceeds with complete stereospecificity and, coupled with the existing methodology for the preparation of chiral propargylic alcohols, provides access to a wide range of optically active allenes (eq 2).[2a]



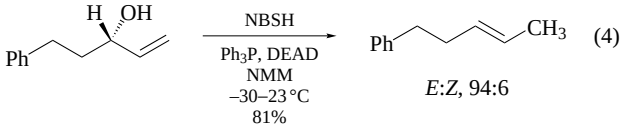
(2)

Reductive Transposition of Allylic Alcohols.[3] In direct analogy to the synthesis of allenes from propargylic alcohols, invertive (Mitsunobu) displacement of allylic alcohols with NBSH followed by warming of the reaction mixture to ambient temperature to induce diazene formation and sigmatropic loss of dinitrogen provides reductively transposed alkenes.[3] This methodology has proven to be highly effective for the reductive 1,3-transposition of a wide variety of allylic alcohols (eq 3).[3]

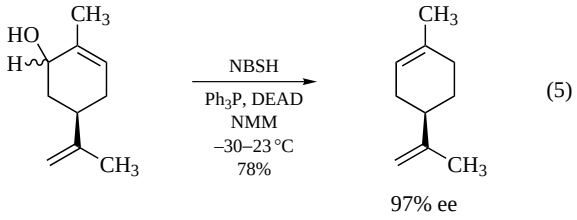


(3)

The rearrangement proceeds with high trans selectivity in the formation of 1,2-disubstituted olefins, an outcome consistent with the minimization of allylic strain during sigmatropic loss of dinitrogen from the allylic diazene intermediates (eq 4). Furthermore, the regioselectivity of the reduction (1,3-transposition versus direct displacement) is complete in all cases studied thus far (eq 5).[3]

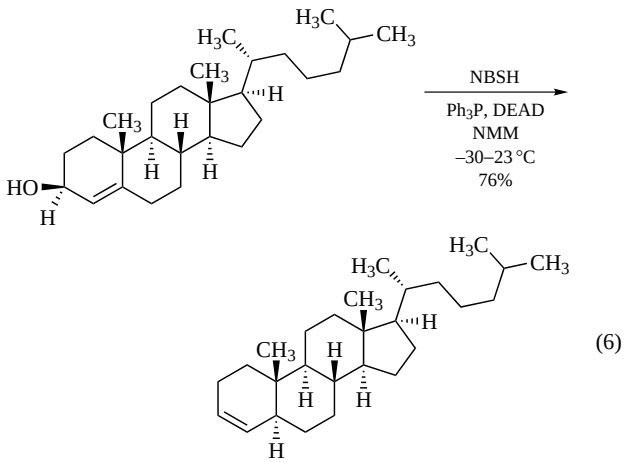


(4)

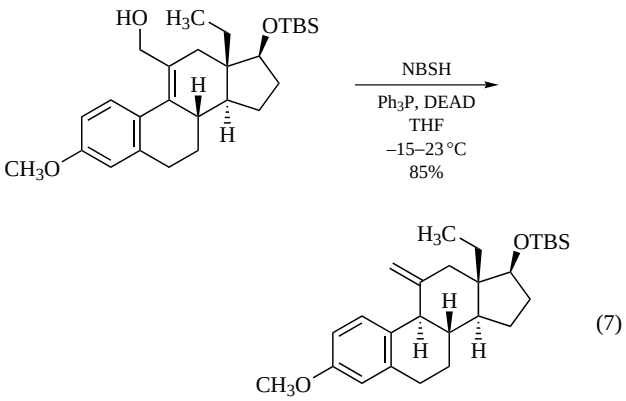


(5)

The invertive nature of the initial displacement reaction may be utilized in a 1,3-transfer of stereochemistry from the hydroxylic center to the β-olefinic carbon (eq 6).[3] Precedence also exists for the use of more distant stereocenters to control the stereoselectivity of hydrogen transfer to the β-olefinic carbon (eq 7).[4]

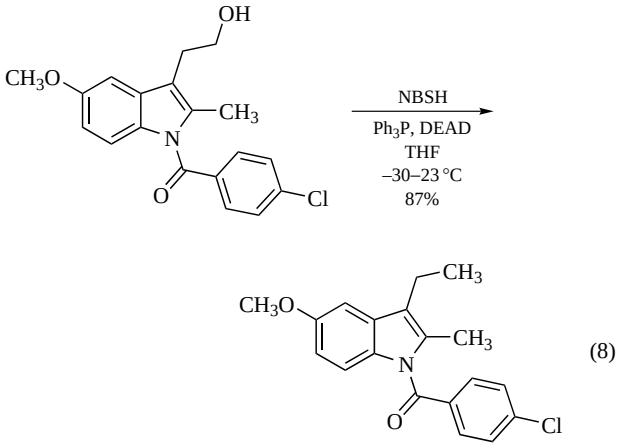


(6)

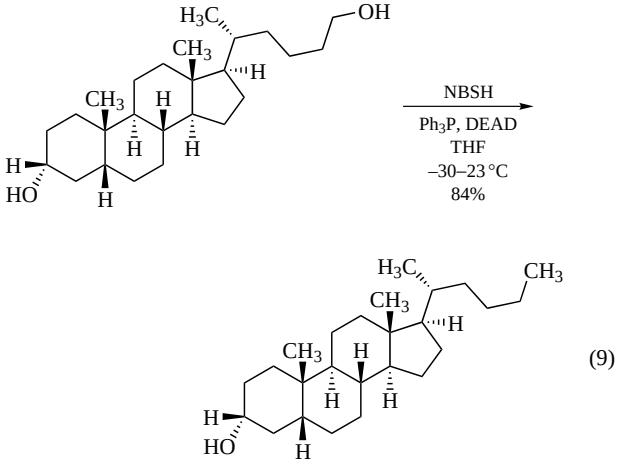


(7)

Deoxygenation of Unhindered Alcohols.[5] The NBSH reagent can be used for the deoxygenation of unhindered primary and secondary alcohols in a single step, without the use of heavy metal hydride reagents and under mild reaction conditions (eq 8).[5] Mitsunobu displacement of saturated alcohols by NBSH followed by in situ elimination of *o*-nitrobenzenesulfinic acid is proposed to provide a monoalkyl diazene intermediate. This monoalkyl diazene intermediate is then proposed to undergo fragmentation by a free-radical mechanism to form dinitrogen and the corresponding alkane.[5] The sensitivity of the initial invertive step to steric effects can be used advantageously in the selective deoxygenation of unhindered alcohols in the presence of other alcohols (eq 9).[5]

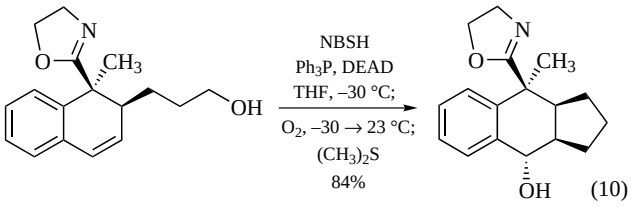


(8)



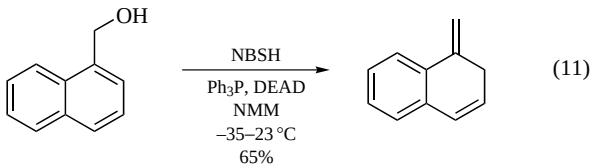
(9)

The proposed free-radical intermediates have been used for ring-formation, for fragmentation, and have been captured by intermolecular trapping (eq 10).[5]



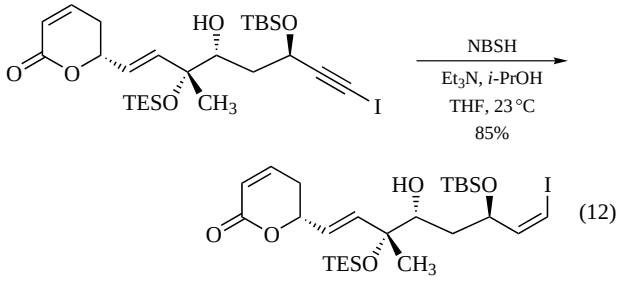
(10)

Deoxygenation of benzylic substrates provides a synthetic route to interesting deconjugated products (eq 11).[5]



(11)

Generation of Diimide. In comparison to other arenesulfonylhydrazines,[6] NBSH undergoes more facile thermal fragmentation (loss of *o*-nitrobenzenesulfinic acid) to form diimide.[1a,7] Simple dissolution of NBSH in water or methanol at ambient temperature leads to the rapid generation of diimide.[1a] The mild nature of this method of diimide generation permits its use with sensitive substrates (eq 12).[8]



(12)

Related Reagents. 2,4-Dinitrobenzenesulfonylhydrazide; Mesitylenesulfonylhydrazide; *p*-Toluenesulfonylhydrazide; 2,4,6-Triisopropylbenzenesulfonylhydrazide.

1. (a) Myers, A. G.; Zheng, B.; Movassaghi, M., *J. Org. Chem.* **1997**, *62*, 750. (b) Dann, A. T.; Davies, W., *J. Chem. Soc.* **1929**, 1050.
2. (a) Myers, A. G.; Zheng, B., *J. Am. Chem. Soc.* **1996**, *118*, 4492. (b) Myers, A. G.; Zheng, B., *Org. Synth.* **1999**, *76*, 178.
3. Myers, A. G.; Zheng, B., *Tetrahedron Lett.* **1996**, *37*, 4841.
4. Corey, E. J.; Huang, A. X., *J. Am. Chem. Soc.* **1999**, *121*, 710.
5. (a) Myers, A. G.; Movassaghi, M.; Zheng, B., *J. Am. Chem. Soc.* **1997**, *119*, 8572. (b) Myers, A. G.; Movassaghi, M.; Zheng, B., *Tetrahedron Lett.* **1997**, *38*, 6569.
6. Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B., *Tetrahedron* **1976**, *32*, 2157.
7. Hünig, S.; Müller, H. R.; Thier, W., *Angew. Chem., Int. Ed.* **1965**, *4*, 271.
8. Chavez, D. E.; Jacobsen, E. N., *Angew. Chem., Int. Ed.* **2001**, *40*, 3667.

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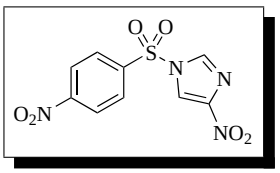
p-Nitrobenzenesulfonyl-4-nitroimidazole



[81006-79-3] $C_9H_6N_4O_6S$ (MW 298.26)
InChI = 1/C9H6N4O6S/c14-12(15)7-1-3-8(4-2-7)20(18,19)11-5-9(10-6-11)13(16)17/h1-6H
InChIKey = COBWHSSAAZPSJT-UHFFFAOYAD

(condensing agent for the triester coupling of nucleotide fragments[1])

Alternate Name: *p*-NBSNI.

Physical Data: mp (sealed tube) 179–185 °C (dec); UV (dioxane) 253 nm.

Solubility: sol pyridine, DMSO; slightly sol dioxane, ethyl acetate.

Form Supplied in: white needles; not available commercially; may be contaminated with *p*-nitrobenzenesulfonic acid.

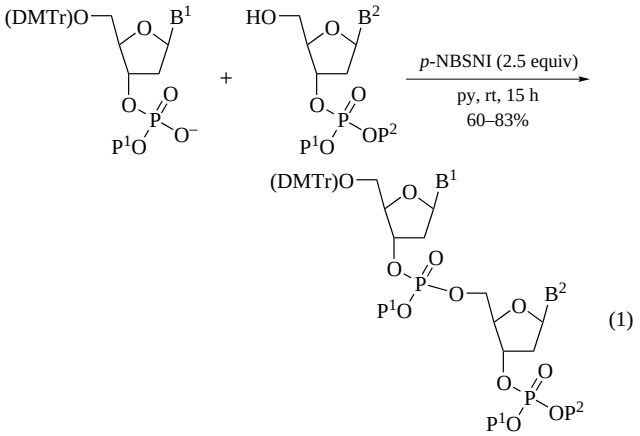
Analysis of Reagent Purity: ^{1}H NMR (60 MHz, DMSO-d_6) δ 8.45 (s, 4H); 8.55 (d, J = 2 Hz, 1H); 9.10 (d, J = 2 Hz, 1H); sulfonic acid impurities are easily detected as higher field signals.

Preparative Method: by treatment of 4-nitroimidazole (1.025 equiv) and *p*-nitrobenzenesulfonyl chloride (1.0 equiv) with triethylamine (1.1 equiv) in dry dioxane at 0 °C.[1]

Purification: recrystallization from ethyl acetate.

Handling, Storage, and Precautions: stable to air and moisture in screw cap bottles at rt for over six months.

Condensing Agent. *p*-Nitrobenzenesulfonyl-4-nitroimidazole has been used as a condensing agent in the triester synthesis of oligonucleotides. The reagent activates the phosphodiester towards attack by the incoming 5′-hydroxyl through formation of a mixed phosphoric–sulfonic anhydride. Typically, the suitably protected nucleotide fragments, in pyridine solution, are treated with *p*-NBSNI (2.5 equiv) and stirred at rt for approximately 15 h. After workup, purification is achieved through two chromatographic separations over silica gel, affording the desired polynucleotide in 60–83% yield (eq 1).[1]



(1)

DMTr = 5′-*O*-dimethoxytrityl; P^1 = *p*-ClC_6H_4; P^2 = cyanoethyl

p-Nitrobenzenesulfonyl-4-nitroimidazole holds the advantage over older reagents, such as triisopropylbenzenesulfonyl chloride, of giving fewer side products resulting from sulfonation of the free 5′-hydroxyl. The long reaction times necessary are a disadvantage and the condensing agents 2,4,6-triisopropylbenzenesulfonyl-1,2,3,4-tetrazole (TPSTe) and 1-(mesitylenesulfonyl)-3-nitro-1,2,4-triazole (MSNT) are preferable.[2]

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1. Leach, C. A.; Tamm, C.; Waldmeier, F., *Helv. Chim. Acta* **1981**, *64*, 2515.
2. Ikehara, M.; Ohtsuka, E.; Uesugi, S.; Tanaka, T. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, 1988; Vol. 1, Chapter 3.

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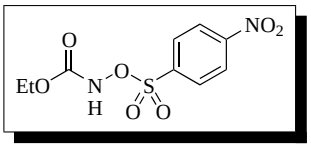
p-Nitrobenzenesulfonyloxyurethane[1]



[2955-74-0] $C_9H_{10}N_2O_7S$ (MW 290.28)

InChI = 1/C9H10N2O7S/c1-2-17-9(12)10-18-19(15,16)8-5-3-7(4-6-8)11(13)14/h3-6H,2H2,1H3,(H,10,12)/f/h10H

InChIKey = XBTJZULRZQBGIT-KZFATGLACP

(generation of ethoxycarbonylnitrene by α-elimination[2,3] under mild conditions, including phase-transfer conditions[4])

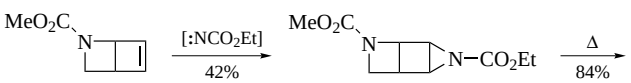
Physical Data: mp 116.4–116.8 °C.

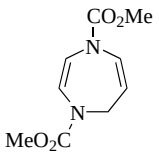
Solubility: sol ether, acetone, $CHCl_3$, CH_2Cl_2, DMSO, DMF, ethyl acetate, alcohols; moderately sol benzene; insol hydrocarbon solvents, CCl_4, H_2O.

Preparative Method: by the reaction of *N*-hydroxyurethane with *p*-nitrobenzenesulfonyl chloride.[2]

Treatment of the title compound with a base such as triethylamine leads to deprotonation followed by α-elimination to generate singlet ethoxycarbonylnitrene.[2,3] The mild conditions required offer an advantage over ethyl azidoformate as a source of the ethoxycarbonylnitrene. The synthetic utility of this nitrene is limited to two types of reactions: (1) aziridination of alkenes and (2) addition to heteroatoms, which is often followed by rearrangement. A common side-reaction is the insertion of the nitrene into C–H bonds. The synthetic utility of the insertion reaction itself is severely limited since ethoxycarbonylnitrene shows poor selectivity toward different types of C–H bonds. The development of procedures to generate this nitrene under phase-transfer conditions has enhanced its utility.[4,5]

Ethoxycarbonylnitrene generated by α-elimination adds to alkenes to give the corresponding aziridines in moderate yields. Thus reaction of ethoxycarbonylnitrene with the strained alkene 2-azabicyclo[2.2.0]hex-5-ene under phase-transfer conditions produces the aziridine in 42% yield (eq 1).[6] Thermolysis of the adduct gives rise to a 1,4-diazepine. This method has been used to access a variety of substituted 1,4-diazepines, 1*H*-1,4-diazepines,[7] and other heterocyclic ring systems.[8]



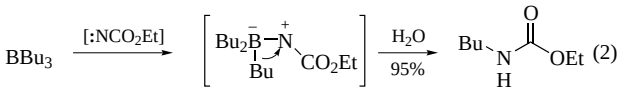


(1)

Addition of ethoxycarbonylnitrene across the double bond of a symmetric propelladiene has been reported to give a mixture of stereoisomeric aziridines in 46% yield.[9] Additions to vinylsilanes

under phase-transfer conditions[10] and to vinyl chlorides[11] produce the corresponding aziridines in moderate yields. Addition to azo compounds yields azimines which, on subsequent photolysis, give the triaziridines.[12] Aziridination of isolated double bonds occurs preferentially over the double bond of allylic ethers.[13] Attempted addition to enamines[14] and allenes[15] gives very low yields of the desired products. Addition to a chiral, optically active enol ether has been reported to proceed in low yield, but with high diastereoselectivity.[16] Additions to allylic and homoallylic acetals have also been reported.[17]

There are few examples of synthetically useful reactions involving addition of ethoxycarbonylnitrene to heteroatoms. Addition to phospholes gives the corresponding iminophospholes in good yield.[18] Addition of ethoxycarbonylnitrene to trialkylboranes gives the corresponding *N*-alkyl carbamates after rearrangement and hydrolysis (eq 2).[19] This procedure allows access to a variety of ethyl *N*-alkylcarbamates in high yields.



Related Reagents. *t*-Butyl Azidoformate; Ethyl Azidoformate.

1. Lwowski, W. In *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic: Orlando, 1984; p 205.
2. Lwowski, W.; Maricich, T. J., *J. Am. Chem. Soc.* **1965**, *87*, 3630.
3. McConaghy, Jr., J. S.; Lwowski, W., *J. Am. Chem. Soc.* **1967**, *89*, 2357.
4. (a) Seno, M.; Namba, T.; Kise, H., *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2975. (b) Seno, M.; Namba, T.; Kise, H., *J. Org. Chem.* **1978**, *43*, 3345.
5. For a comparison of homogeneous and phase-transfer conditions, see:(a) Aitken, R. A.; Gosney, I.; Farries, H.; Palmer, M. H.; Simpson, I.; Cadogan, J. I. G.; Tinley, E. J., *Tetrahedron* **1985**, *41*, 1329. (b) Aitken, R. A.; Gosney, I.; Farries, H.; Palmer, M. H.; Simpson, I.; Cadogan, J. I. G.; Tinley, E. J., *Tetrahedron* **1984**, *40*, 2487.
6. Kurita, J.; Iwata, K.; Sakai, H.; Tsuchiya, T., *Chem. Pharm. Bull.* **1985**, *33*, 4572.
7. Kurita, J.; Iwata, K.; Tsuchiya, T., *Chem. Pharm. Bull.* **1987**, *35*, 3166.
8. (a) Kurita, J.; Kikuchi, K.; Aruga, T.; Tsuchiya, T., *Heterocycles* **1992**, *34*, 685. (b) Kurita, J.; Yoneda, T.; Kakusawa, N.; Tsuchiya, T., *Chem. Pharm. Bull.* **1990**, *38*, 2911. (c) Kurita, J.; Aruga, T.; Tsuchiya, T., *Heterocycles* **1990**, *31*, 1769. (d) Kurita, J.; Sakai, H.; Tsuchiya, T., *Chem. Pharm. Bull.* **1988**, *36*, 2887.
9. Ruttimann, A.; Ginsburg, D., *Tetrahedron* **1976**, *32*, 1009.
10. Lukevics, E.; Dirnens, V. V.; Goldberg, Y. S.; Liepinsh, E. E., *J. Organomet. Chem.* **1986**, *316*, 249.
11. Pellacani, L.; Persia, F.; Tardella, P. A., *Tetrahedron Lett.* **1980**, *21*, 4967.
12. (a) Hoesch, L.; Leuenberger, C.; Hilpert, H.; Dreiding, A. S., *Helv. Chim. Acta* **1982**, *65*, 2682. (b) Leuenberger, C.; Hoesch, L.; Dreiding, A. S., *J. Chem. Soc., Chem. Commun.* **1980**, 1197.
13. Cerichelli, G.; Freddi, A.; Loreto, M. A.; Pellacani, L.; Tardella, P. A., *Tetrahedron* **1992**, *48*, 2495.
14. (a) Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A., *J. Org. Chem.* **1985**, *50*, 5365. (b) Pellacani, L.; Pulcini, P.; Tardella, P. A., *J. Org. Chem.* **1982**, *47*, 5023.
15. Gilbert, J. C.; Bingham, E. M., *J. Org. Chem.* **1975**, *40*, 224.
16. Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A., *Tetrahedron* **1991**, *47*, 5877.
17. Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A., *Tetrahedron Lett.* **1993**, *34*, 4353.
18. Cadogan, J. I. G.; Scott, R. J.; Gee, R. D.; Gosney, I., *J. Chem. Soc., Perkin Trans. 1* **1974**, 1694.
19. (a) Akimoto, I.; Suzuki, A., *Synth. Commun.* **1981**, *11*, 475. (b) Wachter-Jurcsak, N.; Scully, Jr., F. E., *Tetrahedron Lett.* **1990**, *31*, 5261.

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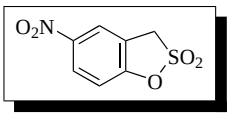
5-Nitro-3*H*-1,2-benzoxathiole *S,S*-Dioxide



[14618-10-1] $C_7H_5NO_5S$ (MW 215.20)

InChI = 1/C7H5NO5S/c9-8(10)6-1-2-7-5(3-6)4-14(11,12)13-7/h1-3H,4H2

InChIKey = NKGKZWZGRMZCMO-UHFFFAOYAQ

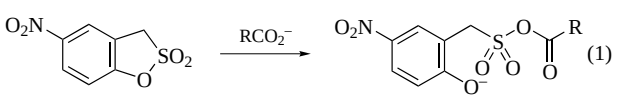
(peptide coupling reagent)

Physical Data: very pale yellow crystals; mp 148.5–149.5 °C.

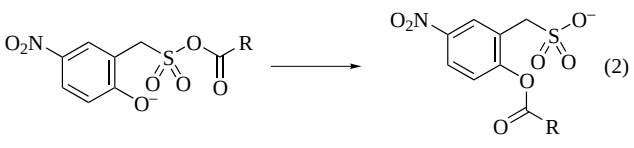
Analysis of Reagent Purity: satisfactory microanalytical data have been reported.[1]

Preparative Method: by nitration of the corresponding sultone.[1]

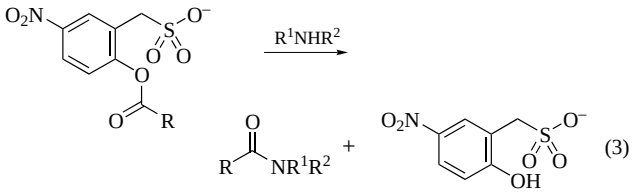
5-Nitro-3*H*-1,2-benzoxathiole *S,S*-dioxide is a peptide coupling reagent.[2,3] Its reactivity derives from the inherent strain present in cyclic five-membered sulfonate esters. These species react with nucleophiles such as carboxylates to form mixed carboxylic sulfonic anhydrides (**1**) (eq 1), which rearrange via an intramolecular acyl transfer to phenyl esters (**2**) (eq 2). When the carboxylate nucleophile in eq 1 is that of an *N*-protected α-amino acid, (**2**) reacts with α-amino esters to give peptides (eq 3 and Table 1). The process offers the advantage that the byproduct of the coupling reaction (sulfonate (**3**)) is water-soluble and, therefore, easily removed from the reaction mixture.



(**1**)



(**2**)



(3)

(**3**)

Table 1 Preparation of dipeptides using 5-nitro-3*H*-1,2-benzoxathiole *S*,*S*-dioxide

Acid	Amine	Yield of *N*-protected dipeptide (%)
Z-Gly-OH	H-Ala-OMe	60
Z-Gly-OH	H-Ser-OMe	60
Z-Phe-OH	H-Gly-OEt	52
Z-Pro-OH	H-Gly-OEt	63
Z-Met-OH	H-Gly-OEt	63
Z-Val-OH	H-Gly-OEt	55
Z-Asn-OH	H-Gly-OEt	40
Z-Ser-OH	H-Gly-OEt	49
Z-Gly-Phe	H-Gly-OEt	56

1. Kaiser, E. T.; Lo, K-W., *J. Am. Chem. Soc.* **1969**, *91*, 4912.
2. Wakselman, M.; Acher, F., *J. Chem. Soc., Chem. Commun.* **1981**, 632.
3. Wakselman, M.; Acher, F., *J. Org. Chem.* **1984**, *49*, 4133.

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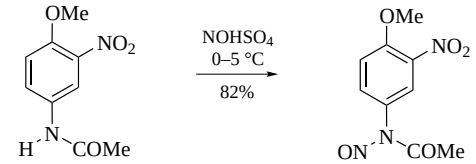
Nitrosylsulfuric Acid

[7782-78-7] HNO_5S (MW 127.09)
InChI = 1/HNO5S/c2-1-6-7(3,4)5/h(H,3,4,5)/f/h3H
InChIKey = VQTGUFBGYOIUFS-TULZNQERCF

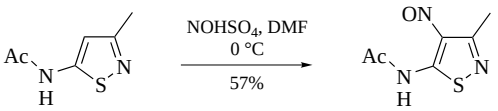
(nitrosating and diazotizing agent; moderate oxidizing agent)

Physical Data: mp 70 °C.
Solubility: sol sulfuric acid; slightly sol acetic acid, acetonitrile, nitromethane, DMF insol most other organic solvents.
Form Supplied in: pale yellow crystals; commercially available.
Preparative Method: dry SO_2 is allowed to pass into a mixture of 98% nitric acid and acetic acid (3:1) at 0 °C; the precipitated $NOHSO_4$ is washed with acetic acid and carbon tetrachloride and dried under vacuum to give the analytically pure reagent.[1]
Handling, Storage, and Precautions: stable at rt; protect from moisture; use in a fume hood.

Nitrosation. Like other nitrosonium salts, namely nitrosonium tetrafluoroborate and $NOPF_6$, nitrosylsulfuric acid is an efficient nitrosating agent. It has been reported that $NOHSO_4$ is superior to nitrosyl chloride for the nitrosation of *N*-acylarylamines such as 4-methoxy-3-nitroacetoanilide and 5-acetamido-6-methoxyquinoline (eq 1).[2] $NOHSO_4$ has also been shown to be more efficient than other classical nitrosating agents such as isopentyl nitrite, phenyl nitrite, and sodium nitrite. For example, successful nitrosation of 3-methyl-5-acetamidoisothiazole was achieved by utilizing nitrosylsulfuric acid in DMF, whereas previous attempts using isopentyl nitrite or sodium nitrite in acetic acid had failed (eq 2).[3] Nitrosation of thebaine in methanol under different conditions using nitrosyl chloride, phenyl nitrite, and $NOHSO_4$ all gave the oxime together with varying amounts of other bimolecular products.[4]

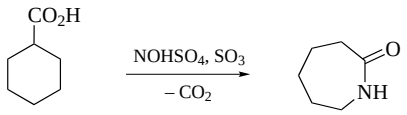


(1)



(2)

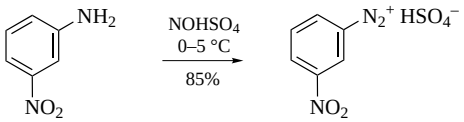
The conversion of cyclohexanecarboxylic acid or cyclohexyl aryl ketone to ε-caprolactam by treatment with $NOHSO_4$ in the presence of SO_3 (eq 3) may involve the nitrosation of an enol and Beckmann rearrangement.[5] Nitrosation of pentamethyleneketene under similar conditions also gives ε-caprolactam.[6] Lactams with 11 and 12 carbon atoms in their rings were obtained in good yields by treating cycloundecanoic acid and cyclododecanoic acid with $NOHSO_4$ in chloroform.[7]



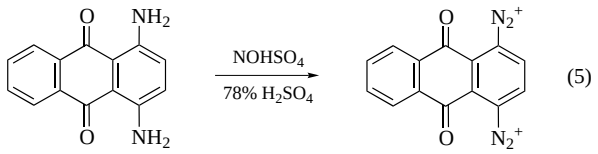
(3)

Diazotization and Related Reactions.

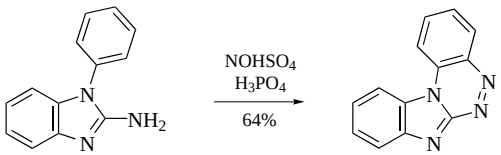
Ar–NH₂ to Ar–N₂⁺. Aromatic amines are readily diazotized by $NOHSO_4$ to give the corresponding diazonium hydrogen sulfates. Although solutions of sodium nitrite in concentrated H_2SO_4, instead of pure $NOHSO_4$, have been used for diazotization, the yields of solid diazonium salts were in some cases relatively poor. For the purpose of preparation of pure diazonium hydrogen sulfates free from other mineral acids and salts, solutions or suspensions of the amines in acetic acid were added to a solution of solid $NOHSO_4$ in acetic acid, then ether was added to precipitate the diazonium salts.[8] Nitrosylsulfuric acid is also suitable for the diazotization of weakly basic amines such as nitroanilines (eq 4) and polynitroanilines,[8,9] tetrafluoroanthranilic acid,[10] aminonaphthoquinones,[11] 1,4-diaminoanthraquinones (eq 5)[12] and 2-cyano-4-nitroaniline.[13] In some cases the diazonium salts formed undergo intramolecular coupling with aryl rings to give azo compounds (eq 6).[14,15]



(4)

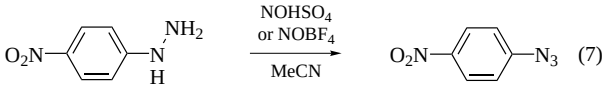


(5)



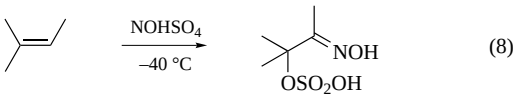
(6)

***Ar–NHNH*$_2$ *to Ar–N*$_3$.** Aryl and acyl hydrazines are converted to azides in good yields on treatment with an equimolar amount of $NOHSO_4$ or $NOBF_4$ (eq 7).[16]

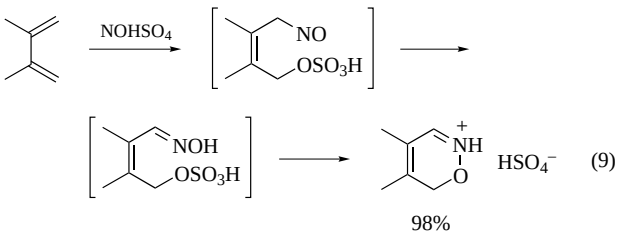


(7)

Addition to Alkenes and Dienes. $NOHSO_4$ adds to trisubstituted alkenes to give β-sulfatooximes (eq 8), which are relatively unstable and react readily with nucleophiles such as piperidine, MeOH, or AcOK to give the corresponding α-substituted oximes.[17] Conjugated dienes react with $NOHSO_4$ at low temperature in liquid SO_2, giving 1,4-addition products which spontaneously cyclize to 6*H*-1,2-oxazine hydrogen sulfates (eq 9).[18]

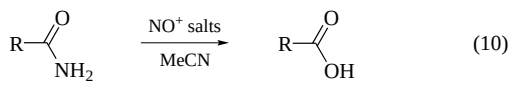


(8)

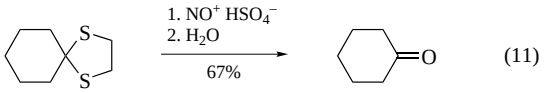


(9)

Other Applications. Amides and sulfonamides are converted to the corresponding acids by $NOHSO_4$ and other nitrosonium salts at low temperature in acetonitrile or nitromethane (eq 10).[19] Sterically hindered amides also react with ease and good yields, although higher reaction temperatures are needed. A mild cleavage of ethylene dithioacetals to ketones has been achieved with $NOHSO_4$ in methylene chloride or $NaNO_2$ in aq CF_3CO_2H (eq 11).[20]

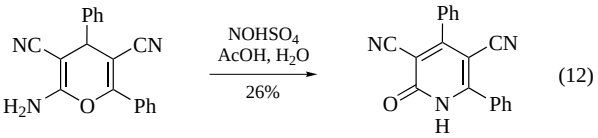


(10)



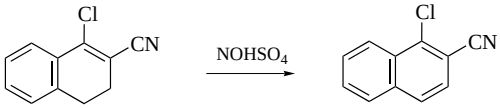
(11)

The treatment of 2-amino-4*H*-pyrans with nitrosylsulfuric acid brings about their transformation into 2-pyridones (eq 12).[21]



(12)

All nitrosonium ions are in principle hydride-abstracting agents, and nitrosylsulfuric acid has occasionally been used as a dehydrogenating agent (eq 13).[22]



(13)

1. Richards, G. W.; Woolf, A. A., *J. Chem. Soc.* **1968**, 470.
2. Ahmad, Y.; Qureshi, M. I.; Baig, M. I., *Can. J. Chem.* **1967**, *45*, 1539.
3. Taylor, E. C.; Wachsen, E., *J. Org. Chem.* **1978**, *43*, 4154.
4. Bentley, K. W.; Kirby, G. W.; Price, A. P.; Singh, S., *J. Chem. Soc., Perkin Trans. 1* **1972**, 302.
5. (a) Ogata, Y.; Furuya, Y.; Ito, M., *J. Am. Chem. Soc.* **1963**, *85*, 3649. (b) Tokura, N.; Kawahara, T.; Sato, T., *Bull. Chem. Soc. Jpn.* **1965**, *38*, 849.
6. (a) Giuffre, L.; Tempesti, E; Sioli, G.; Fornaroli, M.; Airoldi, G., *Chem. Ind. (London)* **1971**, 1098. (b) Giuffre, L.; Tempesti, E.; Fornaroli, M.; Sioli, G.; Mattone, R.; Airoldi, G., *Hydrocarbon Process* **1973**, *52*, 199.
7. Ziegenbein, W.; Lang, W., *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 149.
8. Piercey, M. R.; Ward, E. R., *J. Chem. Soc.* **1962**, 3841.
9. Röbisch, G.; Süptitz, H., *J. Prakt. Chem.* **1978**, *320*, 1047.
10. Hayashi, S.; Ishikawa, N., *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2909.
11. Mosby, W. L.; Silva, M. L., *J. Chem. Soc.* **1964**, 3990.
12. Law, K.-Y.; Tarnawskyj, I. W.; Kaplan, S., *Can. J. Chem.* **1991**, *69*, 1183.
13. Ramdas, S. R.; Ramana, D. V.; Chaudhuri, A. P., *Indian J. Chem., Sect. B* **1973**, *11*, 400.
14. Kolodyazhnaya, S. N.; Simonov, A. M.; Uryukina, I. G., *Khim. Geterotsikl. Soedin.* **1972**, 1690.
15. Kolodyazhnaya, S. N.; Simonov, A. M.; Zheltikova, N. N.; Pozharskii, A. F., *Khim. Geterotsikl. Soedin.* **1973**, 714.
16. Pozsgay, V.; Jennings, H. J., *Tetrahedron Lett.* **1987**, *28*, 5091.
17. Kisan, W.; Pritzkow, W., *J. Prakt. Chem.* **1978**, *320*, 59.
18. Klamann, D.; Fligge, M.; Weyerstahl, P.; Kratzer, J., *Chem. Ber.* **1966**, *99*, 556.
19. Olah, G. A.; Olah, J. A., *J. Org. Chem.* **1965**, *30*, 2386.
20. Olah, G. A.; Narang, S. C.; Salem, G. F.; Gupta, B. G. B., *Synthesis* **1979**, 273.
21. Seoane, C.; Soto, J. L.; Zamorano, P.; Quinteiro, M., *J. Heterocycl. Chem.* **1981**, *18*, 309.
22. Gorelik, M. V.; Lomzakova, V. I., *Zh. Org. Khim.* **1978**, *14*, 1051.

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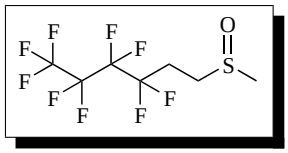
1,1,1,2,2,3,3,4,4-Nonafluoro-6-(methanesulfinyl)hexane



[357604-65-0] $C_7H_7F_9OS$ (MW 310.18)

InChI = 1/C7H7F9OS/c1-18(17)3-2-4(8,9)5(10,11)6(12,13)7(14,15)16/h2-3H2,1H3

InChIKey = WJDLEZALBASYOV-UHFFFAOYAW

(the title reagent is best suited as an alternative to DMSO for the oxidation of primary alcohols to aldehydes, secondary alcohols to ketones, and lactols to lactones to avoid the malodorous DMS. Another advantage of this reagent is that it can be recycled)[1,2]

Alternate Name: fluorous DMSO.

Physical Data: white crystals, mp 46 °C.

Solubility: soluble in CH_2Cl_2, perfluorohexanes (FC-72).

Form Supplied in: pure compound, commercially available.

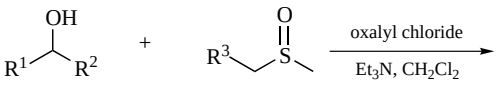
Analysis of Reagent Purity: NMR, elemental analysis, mp.

Preparative Methods: for information on methods of preparation, see refs 1 and 2.

Purity: liquid/liquid extraction.

Handling, Storage, and Precaution: avoid contact with skin; store in a cool and dry place; keep container closed when not in use. Keep away from heat, moisture, and incompatible materials (for example, acyl halides).

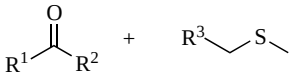
Introduction. The combination of DMSO, oxalyl chloride, and triethylamine (TEA) (Swern oxidation[3]) has been widely used for the oxidation of primary alcohols to aldehydes and secondary alcohols to ketones due to the mild reaction conditions and the tolerance of a broad range of functional groups (eq 1). However, the malodorous dimethylsulfide (DMS) derived from DMSO makes the Swern oxidation unpleasant to conduct, especially on a large scale. Reagent **1** is designed as an alternative to DMSO by attaching a fluorous[4] alkyl chain to one of the methyl groups. The introduction of the fluorous portion has two important consequences.



R^1, R^2 = alkyl, aryl, or H

DMSO (R^3 = H)

1 ($R^3 = C_4F_9CH_2$)



(1)

DMS (R^3 = H)

2 ($R^3 = C_4F_9CH_2$)

First, the corresponding sulfide **2** has relatively low volatility and is not malodorous. Second, fluorous sulfide **2** can be easily separated from the reaction mixture by continuous fluorous/organic liquid-liquid extraction and then oxidized to **1** with hydrogen peroxide for reuse. In addition, sulfoxide **1** has similar reactivities and compatibility as DMSO with a variety of functional groups due to the relatively inert nature of the fluorous subunit.

Besides reagent **1**, several other DMSO substitutes have been reported (Figure 1) for the environmentally benign version of the Swern oxidation. Similar to **1**, sulfoxides **3**, **4**, **5**, and **6** and their corresponding sulfides are odorless.[5–8] Sulfoxide **3** is very close to **1** in terms of reactivity and compatibility to functional groups. However, the separation of the reduced sulfide **3** from the reaction mixture calls for a time-consuming column chromatography, while the separation of **2** only requires liquid-liquid extraction. Although the polymer-supported sulfoxides **4** and **5** can be recycled by oxidation and a simple filtration, the low loading capacities of these two reagents make them less efficient than fluorous sulfoxide **1**. Reagent **1** also has an advantage over sulfoxide **6** since the presence of the carboxylic acid group in **6** limits its reaction scope.

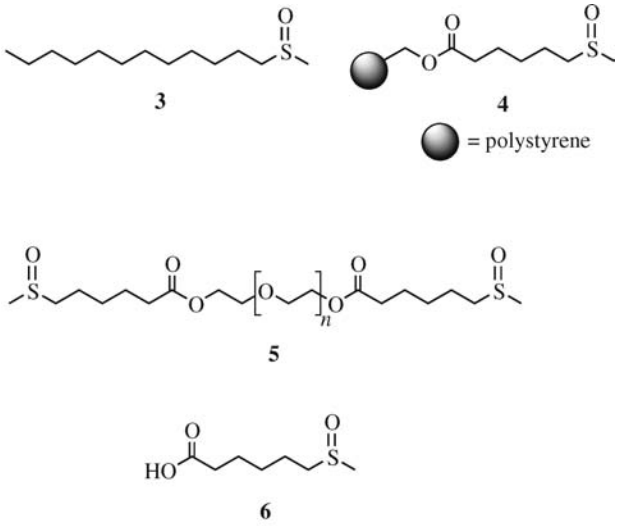
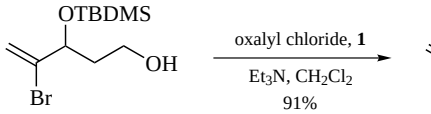
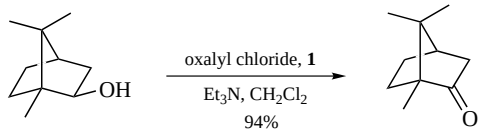


Figure 1 Some other DMSO substitutes used for Swern oxidations

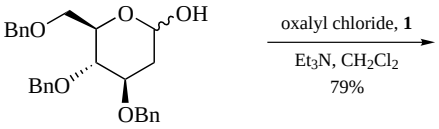
Applications. Twelve examples are given in ref 2 to demonstrate the applications of fluorous sulfoxide **1** for the oxidation of primary alcohols to aldehydes (eq 2), secondary alcohols to ketones (eq 3), and lactols to lactones (eq 4). The mild reaction conditions and the tolerance of a broad range of functional groups, which are characteristic of the original Swern oxidation protocol, are retained. The reactions are generally completed in 2–3 h. The desired aldehydes, ketones, or lactones are isolated in 84–90% yields, while fluorous sulfide **2** is separated from the reaction mixture by continuous extraction and is oxidized to sulfoxide **1** for reuse.

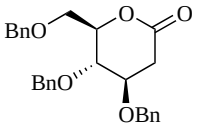


(2)



(3)





(4)

Experimental Protocol. The experimental protocol for using fluorous sulfoxide **1** in the Swern oxidation is similar to the original one[3] where DMSO is used except for the work-up details.[1,2] The reactions are typically run in anhydrous CH_2Cl_2 at $-30\,^{\circ}C$ for 1–2 h and then warmed to room temperature for 1 h. The reaction mixture is diluted with H_2O, washed with saturated NH_4Cl solution, and then extracted with CH_2Cl_2. CH_2Cl_2 is subsequently removed carefully under vacuum in a cold-water bath. The resulting residue is dissolved in toluene and extracted continuously with FC-72 instead of being used directly for purification by column chromatography on silica gel. The FC-72 layer is then treated with hydrogen peroxide to regenerate **1** and the toluene layer is concentrated to yield aldehydes, ketones, or lactones after purification by column chromatography on silica gel.

Related Reagents. 1,1,1,2,2,3,3,4,4,5,5,6,6-Tridecafluoro-8-methanesulfinyloctane; see reagents in Figure 1.[1,2]

1. Crich, D.; Neelamkavil, S., *J. Am. Chem. Soc.* **2001**, *123*, 7449.
2. Crich, D.; Neelamkavil, S., *Tetrahedron* **2002**, *58*, 3865.
3. Mancuso, A. J.; Huang, S. L.; Swern, D., *J. Org. Chem.* **1978**, *43*, 2480.
4. Gladysz, J. A.; Curran, D. P., *Tetrahedron* **2002**, *58*, 3823.
5. Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T., *Tetrahedron Lett.* **2001**, *42*, 9207.
6. Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C., *J. Org. Chem.* **1998**, *63*, 2407.
7. Liu, Y.; Vederas, J. C., *J. Org. Chem.* **1996**, *61*, 7856.
8. Nishide, K.; Ohsugi, S.; Fudesaka, M.; Kodama, S.; Node, M., *Tetrahedron Lett.* **2002**, *43*, 5177.

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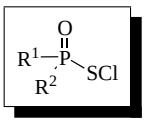
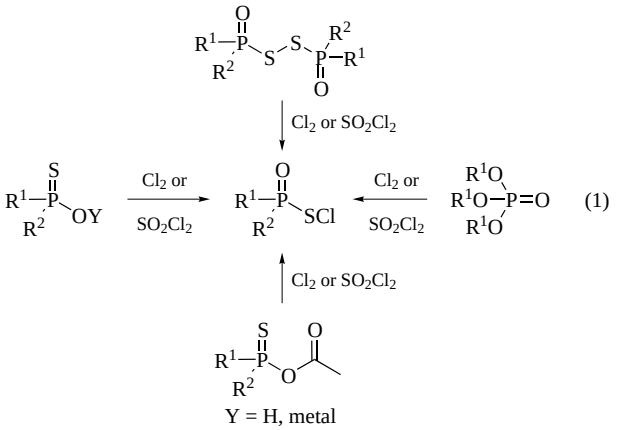
Oxodimethoxyphosphoranesulfenyl Chloride[1]



(**1**; $R^1 = R^2 = OMe$)
[13894-35-4] $C_2H_6ClO_3PS$ (MW 176.57)
InChI = 1/C2H6ClO3PS/c1-5-7(4,6-2)8-3/h1-2H3
InChIKey = UJOKLHUOWLMERO-UHFFFAOYAY
(**2**; $R^1 = R^2 = OEt$)
[1186-08-9] $C_4H_{10}ClO_3PS$ (MW 204.63)
InChI = 1/C4H10ClO3PS/c1-3-7-9(6,10-5)8-4-2/h3-4H2,1-2H3
InChIKey = LIMPRBWQNDVVEY-UHFFFAOYAJ
(**3**; $R^1 = R^2 = O$-*i*-Pr)
[55655-36-2] $C_6H_{14}ClO_3PS$ (MW 232.69)
InChI = 1/C6H14ClO3PS/c1-5(2)9-11(8,12-7)10-6(3)4/h5-6H, 1-4H3
InChIKey = YAVBHNTURIPKRJ-UHFFFAOYAG

(reacts as a pseudohalogen;[1] adds across alkenes and alkynes with little regioselectivity;[2–5] can thiophosphorylate aldehydes and ketones α to the carbonyl[6])

Physical Data: (**1**) bp 50 °C/0.06 mmHg. (**2**) bp 50 °C/0.2 mmHg. (**3**) bp 86 °C/2 mmHg.
Solubility: sol CH_2Cl_2, CCl_4, benzene, diethyl ether, THF.
Form Supplied in: yellow liquids; not commercially available.
Preparative Methods: prepared from a variety of different precursors using the procedures shown in eq 1.[1]

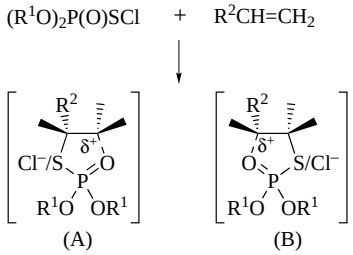


(1)

(**a**) $R^1 = R^2$ = O-alkyl, O-aryl
(**b**) R^1 = O-alkyl, O-aryl; R^2 = alkyl, aryl
(**c**) $R^1 = R^2$ = alkyl, aryl

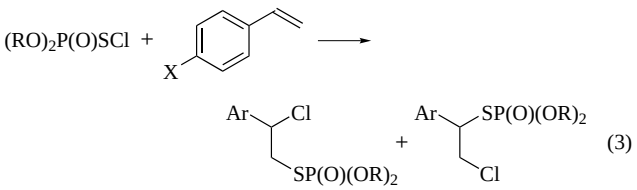
Handling, Storage, and Precautions: stability is in the order: phosphoro, $(R^1O)_2P–$ > phosphono, $(R^1O)R^2P–$ > phosphino, $R^1R^2P–$. Phosphoryl derivatives are quite stable and may be distilled under vacuum. They decompose upon storage, even at low temperatures, and are often prepared and used in situ. Phosphono derivatives lose sulfur on heating and phosphino derivatives lose sulfur at 20 °C and are only moderately stable at 0 °C.

Additions to Alkenes. The addition of phosphoranesulfenyl chlorides to alkenes is not as regioselective as similar additions of methanesulfenyl chloride or other alkyl- and arylsulfenyl chlorides where anti-Markovnikov products tend to predominate.[2] This is due to the fact that additions of phosphoranesulfenyl chlorides proceed by an Ad_E2 mechanism which does not necessarily involve a thiiranium ion intermediate, in contrast to those of *C*-sulfenyl chlorides.[3,7] The electron-withdrawing property of the phosphorus impairs the bridging ability of the sulfur atom sufficiently to make the intermediate possess more carbonium ion character, with the chloride counterion more closely associated with the sulfur atom.[2,8] Also, the oxygen atom attached to phosphorus may contribute to stabilization of cationic intermediates (eq 2).[3]



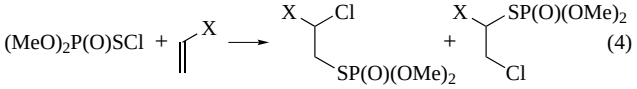
(2)

The additional regiochemical dependence of these additions on the steric and electronic effects of the alkene and phosphorus substituents can contribute to the low regioselectivity of these reactions (eqs 3 and 4).[3,4]



(3)

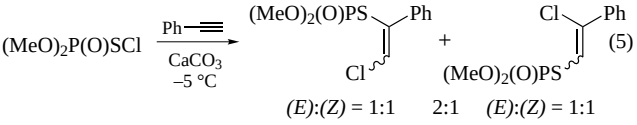
R = Me X = Cl, Br, CH_2Cl, NO_2 100:0
R = *i*-Pr X = Cl, Br, CH_2Cl, NO_2 50:50



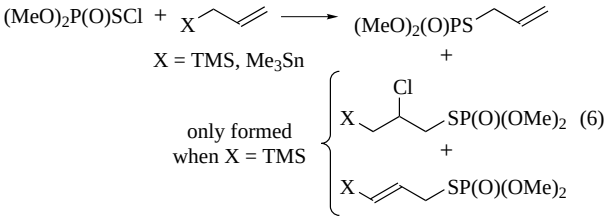
(4)

X = CN, SO_2Me, $SiEt_2Me$ 0:100
X = Ph 100:0
X = CO_2Me 66:34
X = $P(O)(OEt)_2$ 50:50

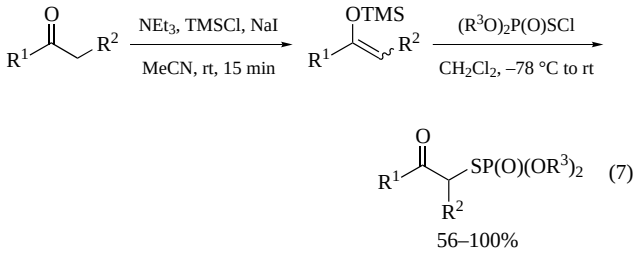
Addition to Alkynes. The substantial amount of *cis* product produced in the addition of phosphoranesulfenyl chlorides to alkynyl compounds is evidence for an unsymmetrical reaction intermediate in which an appreciable amount of positive charge is localized on one carbon atom (eq 5).[5]



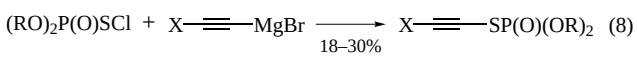
Addition to Allylsilanes and Allylstannanes. Reaction of phosphoranesulfenyl chlorides with allylsilanes and allylstannanes is similar, with both giving the products of an S_E2' mechanism (although this mechanistic pathway has not been proven).[5] In the case of allylsilanes, however, other products are also formed (eq 6).



Reaction with Aldehydes and Ketones. Aldehydes and ketones may be thiophosphorylated α to the carbonyl by reaction of silyl enol ethers with phosphoranesulfenyl chlorides (eq 7).[6]

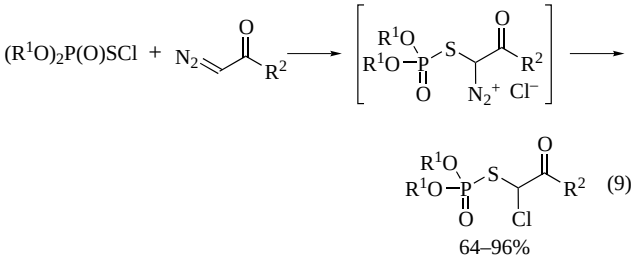


Reaction with Acetylide Anions. The preparation of *S*-ethynyl esters of thiophosphoric acids occurs in moderate yield by the reaction of phosphoranesulfenyl chlorides with ethynylmagnesium bromide (eq 8).[9]



R = Et, Pr, Bu
X = H, Bu, CH_2SEt, CH_2Bu, $S(O)P(OEt)_2$

Reaction with α-Diazo Ketones. Reaction of phosphoranesulfenyl chlorides with α-diazo ketones may be performed in CH_2Cl_2 or ether at −15 °C, or in benzene at 6 °C. Since these reaction conditions preclude the formation of a carbene intermediate, the reaction is thought to proceed via a diazonium cation to give α-chloro-substituted esters of thiophosphoric acid (eq 9).[10]



1. (a) Capozzi, G.; Modena, G.; Pasquato, L. In *The Chemistry of Sulphenic Acids and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1990; p 403. (b) Kuehle, E. *The Chemistry of Sulphenic Acids*; Theime: Stuttgart, 1973.
2. Mueller, W. H.; Rubin, R. M.; Butler, P. E., *J. Org. Chem.* **1966**, *31*, 3537.
3. Kutyrev, G. A.; Sadykova, L. A.; Cherkasov, R. A., *J. Gen. Chem. USSR (Engl. Transl.)* **1991**, *61*, 1821.
4. Kutyrev, G. A.; Vinokurov, A. I.; Ishmaeva, E. A.; Shakirov, I. K.; Shagidullin, R. R.; Cherkasov, R. A.; Pudovik, A. N., *J. Gen. Chem. USSR (Engl. Transl.)* **1979**, *49*, 458.
5. Kutyrev, G. A.; Kapura, A. A.; Cherkasov, R. A.; Pudovik, A. N., *J. Gen. Chem. USSR (Engl. Transl.)* **1985**, *55*, 1919.
6. Dybowski, P.; Skowronska, A., *Synthesis* **1990**, 609.
7. (a) Kutyrev, G. A.; Vinokurov, A. I.; Cherkasov, R. A.; Pudovik, A. N., *Dokl. Akad. Nauk SSSR* **1979**, *245*, 306. (b) Kutyrev, G. A.; Vinokurov, A. I.; Istomina, B. I.; Cherkasov, R. A.; Pudovik, A. N., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, *51*, 837.
8. Mueller, W. H., *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 482.
9. Godovikov, N. N.; Vikhreva, L. A.; Babsheva K. K.; Sherstobitov, O. E.; Balashova, E. K.; Kugusheva, L. I.; Rozengart, V. I.; Brestkin, A. P.; Kabachnik, M. I., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 1453.
10. (a) Khaskin, B. A.; Makhaeva, G. F.; Torgasheva, N. A.; Ishmuratov, A. S.; Yankovskaya, V. L.; Fetisov, V. I.; Malygin, V. V.; Martynov, I. V., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 2508. (b) Khaskin, B. A.; Ishmuratov, A. S.; Torgasheva, N. A., *J. Gen. Chem. USSR (Engl. Transl.)* **1991**, *61*, 993.

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P

Pentafluorosulfanyl Chloride

[13780-57-9] ClF_5S (MW 162.51)
InChI = 1/ClF5S/c1-7(2,3,4,5)6
InChIKey = GSYNTTDHMKSMFY-UHFFFAOYAF

(reagent used for the incorporation of the SF_5 group into organic molecules)

Physical Data: mp −64 °C; bp −21 °C.
Solubility: soluble in most organic solvents.
Form Supplied in: colorless gas packaged in cylinders, commercially available.
Analysis of Reagent Purity: IR,[1] ^{19}F NMR,[2] Raman spectrum.[1a,1b,3]
Preparative Methods: there are several practical methods of preparation of pentafluorosulfanyl chloride. It could be formed rapidly (1 h) and in high yield (92%) by room-temperature reaction of SF_4 with ClF in the presence of activated CsF (eq 1).[4] The compound is also prepared from the reaction of sulfur tetrafluoride (SF_4), chlorine, and CsF in high yield at elevated temperatures (eq 2).[5] A high yield and inexpensive preparation of SF_5Cl from sulfur tetrafluoride, Cl_2, and KF has also been described, but a much longer reaction time is required at relatively high temperatures (eq 3).[6]

$$SF_4 + ClF \xrightarrow[\text{rt, 92\%}]{\text{CsF}} SF_5Cl \quad (1)$$

$$SF_4 + Cl_2 + CsF \xrightarrow[60\%]{125\ ^\circ C,\ 2\ h} SF_5Cl + CsCl \quad (2)$$

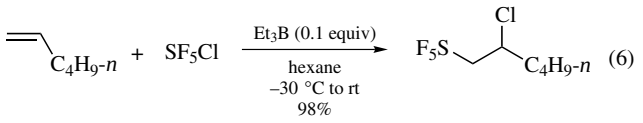
$$SF_4 + Cl_2 + KF \xrightarrow[90\%]{\text{75 °C, 3 d; then 150 °C, 4–6 d}} SF_5Cl + KCl \quad (3)$$

Purity: fractionated through a low-temperature column.
Handling, Storage, and Precautions: pentafluorosulfanyl chloride is stable at room temperature. Since it is toxic, it should be used in a fume hood.

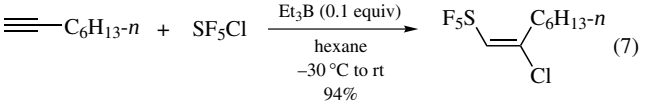
Reactions with Alkenes, Alkynes, and Allenes. Pentafluorosulfanyl chloride has been used in a free radical chain addition process to alkenes and alkynes.[7] These free radical chain addition reactions have been accomplished thermally (eq 4)[8] in an autoclave or via a room-temperature gas-phase or low-temperature solution-phase photochemical process (eq 5).[9] A variety of alkenes and alkynes react with SF_5Cl to give the addition product.[10] Recently, Et_3B has been used successfully at −30 °C in hexane as a catalytic initiator to provide a convenient, regiospecific, and highly stereoselective addition of SF_5Cl in high yield to a variety of alkenes and alkynes (eqs 6 and 7).[11]

$$SF_5Cl + H_2C{=}CHCH_3 \xrightarrow[\text{autoclave, 78\%}]{\text{90 °C, 10 h}} SF_5CH_2CHClCH_3 \quad (4)$$

$$SF_5Cl + HFC{=}CF_2 \xrightarrow{h\nu} \underset{31\%}{SF_5CHFCF_2Cl} + \underset{12\%}{SF_5CF_2CHFCl} \quad (5)$$



(6)



(7)

Pentafluorosulfanyl chloride has also been found to react with tetrafluoroallene to give the addition product in low yield (eq 8).[12]

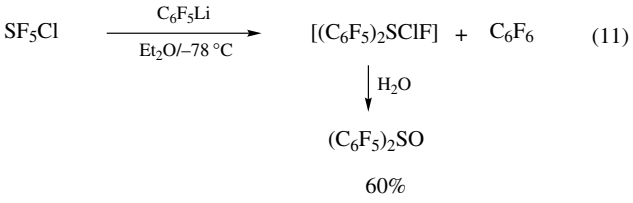
$$F_2C{=}C{=}CF_2 + SF_5Cl \xrightarrow[20\%]{100\ ^\circ C,\ 3\ h} SF_5CF_2ClC{=}CF_2 \quad (8)$$

Reactions with Nitriles. Irradiation of a mixture of SF_5Cl with perfluoronitriles has yielded the $F_5SN{=}C<$ structure (eq 9). Conversions to these novel perfluoroazomethines range from 30% to 40%.[4,13]

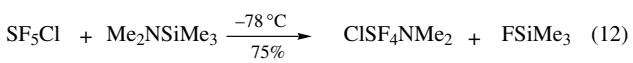
$$SF_5Cl + R_fCN \xrightarrow{h\nu} R_fClC{=}NSF_5 \quad (9)$$

Reactions with Various Nucleophiles. Although in the radical reaction of SF_5Cl with olefins, alkynes, or perfluoronitriles, the integrity of the SF_5 moiety is maintained; reactions of SF_5Cl with nucleophilic reagents often involve defluorination of the sulfur group. A variety of reactive nucleophiles react with pentafluorosulfanyl chloride to give unusual products of synthetic utility. Reaction of trifluorothiomethyllithium with pentafluorosulfanyl chloride forms a mixture of bis(trifluoromethyl)trisulfane, CF_3SCl, and bis(trifluoromethyl)disulfane (eq 10).[14] Reaction of pentafluorosulfanyl chloride with C_6F_5Li gives bis(pentafluorophenyl)sulfoxide after quenching with water (eq 11).[14] Reaction of pentafluorosulfanyl chloride with dimethylaminotrimethylsilane affords $ClSF_4NMe_2$ (eq 12).[15] SF_5Cl undergoes smooth reaction with $LiN{=}C(CF_3)_2$, resulting in the replacement of the sulphur-fluorine bond by the sulphur-nitrogen multiple bond, accompanied by a fluorine atom shift (eq 13).[16]

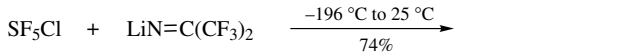
$$SF_5Cl \xrightarrow[Et_2O/-78\ ^\circ C]{CF_3SLi} \underset{5\%}{(CF_3)_2S_3} + \underset{14\%}{(CF_3)_2S_2} + \underset{41\%}{CF_3SCl} \quad (10)$$



(11)



(12)



$ClF_3S{=}NCF(CF_3)_2$ (13)

1. (a) Griffiths, J. E., *Spectrochim. Acta.* **1967**, *A23*, 2145. (b) Smardzewski, R. R.; Noftle, R. E.; Fox, W. B., *J. Mol. Spectrosc.* **1976**, *62*, 449. (c) Roberts, H. L.; Ray, N. H., *J. Chem. Soc.* **1960**, 665.
2. Merrill, C. I.; Williamson, S. M.; Cady, G. H.; Eggers, D. F., *Inorg. Chem.* **1962**, *1*, 215.
3. Noftle, R. E.; Smardzewski, R. R.; Fox, W. B., *Inorg. Chem.* **1977**, *16*, 3380.
4. Tullock, C. W.; Coffman, D. D.; Muetterties, E. L., *J. Am. Chem. Soc.* **1964**, *86*, 357.
5. Schack, C. J.; Wilson, R. D.; Warner, M. G., *J. Chem. Soc., Chem. Commun.* **1969**, 1110
6. Jonethal, U.; Kuschel, R.; Seppelt, K., *J. Fluorine Chem.* **1998**, *88*, 3.
7. Sidebottom, H. W.; Tedder, J. M.; Walton, J. C., *Trans. Faraday. Soc.* **1969**, *65*, 2103.
8. Case, J. R.; Ray, N. H.; Roberts, H. L., *J. Chem. Soc.* **1961**, 2066.
9. Banks, R. E.; Haszeldine, R. N.; Morton, W. D., *J. Chem. Soc.* **1969**, 1947.
10. (a) Case, J. R.; Ray, N. H.; Roberts, H. L., *J. Chem. Soc.* **1961**, 2070. (b) Winter, R.; Gard, G. L., *J. Fluorine Chem.* **1994**, *66*, 109. (c) Berry, A. D.; Fox, W. B., *J. Fluorine Chem.* **1975**, *6*, 175. (d) Sidebottom, H. W.; Tedder, J. M.; Walton, J. C., *J. Chem. Soc., Chem. Commun.* **1970**, 253. (e) DeMarco, R. A.; Fox, W. B., *J. Fluorine Chem.* **1978**, *12*, 137. (f) Potter, B.; Seppelt, K., *Inorg. Chem.* **1982**, *21*, 3147.
11. Ait-Mohand, S.; Dolbier, W. R., Jr, *Org. Lett.* **2002**, *4*, 3013.
12. Witucki, E. F., *J. Fluorine Chem.* **1982**, *20*, 803.
13. (a) Nielsen, J. B.; Thrasher, J. S., *J. Fluorine Chem.* **1990**, *48*, 407. (b) Patel, N. R.; Kirchmeier, R. L.; Shreeve, J. M., *Inorg. Chem.* **1993**, *32*, 4802.
14. Kitazume, T.; Shreeve, J. M., *J. Am. Chem. Soc.* **1978**, *100*, 492.
15. Kitazume, T.; Shreeve, J. M., *J. Am. Chem. Soc.* **1977**, *99*, 3690.
16. Kitazume, T.; Shreeve, J. M., *J. Chem. Soc., Chem. Commun.* **1976**, 982.

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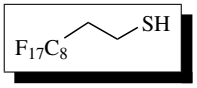
1*H*,1*H*,2*H*,2*H*-Perfluorodecanethiol



[34143-74-3] $C_{10}H_5F_{17}S$ (MW 480.19)

InChI = 1/C10H5F17S/c11-3(12,1-2-28)4(13,14)5(15,16)6(17,18)7(19,20)8(21,22)9(23,24)10(25,26)27/h28H,1-2H2

InChIKey = URJIJZCEKHSLHA-UHFFFAOYAK

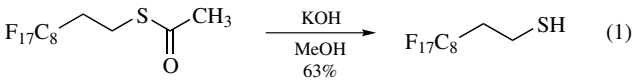
(fluorous thiol used as scavenger, tagging agent, and for a wide array of nucleophilic and free radical reactions)

Physical Data: bp 82 °C/12 mm Hg, d 1.64.

Solubility: soluble in ethyl acetate, THF, dichloromethane, and other organic solvents.

Form Supplied in: colorless liquid; commercially available from Fluorous Technologies, Inc. (www.fluorous.com) and other commercial sources.

Preparative Methods: fluorous thiol can be synthesized from the fluorous thioester as shown in eq 1. A solution of KOH (17.0 g, 0.30 mol) in 350 mL of MeOH was degassed in a sonicator for 30 min. To this solution was added the fluorous thioester (135.0 g, 0.25 mol) in 50 mL of MeOH (degassed) dropwise at 0 °C. The reaction mixture was allowed to warm up to 25 °C in 2 h after the addition was complete. Upon completion of the reaction (checked by TLC), saturated aq NH_4Cl was added, followed by acidification to *p*H ~ 6 with conc. HCl and extraction with hexanes (3 x 250 mL). The combined hexane layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was distilled (bp 82 °C/12 mm Hg) to give the product as a clear colorless oil.



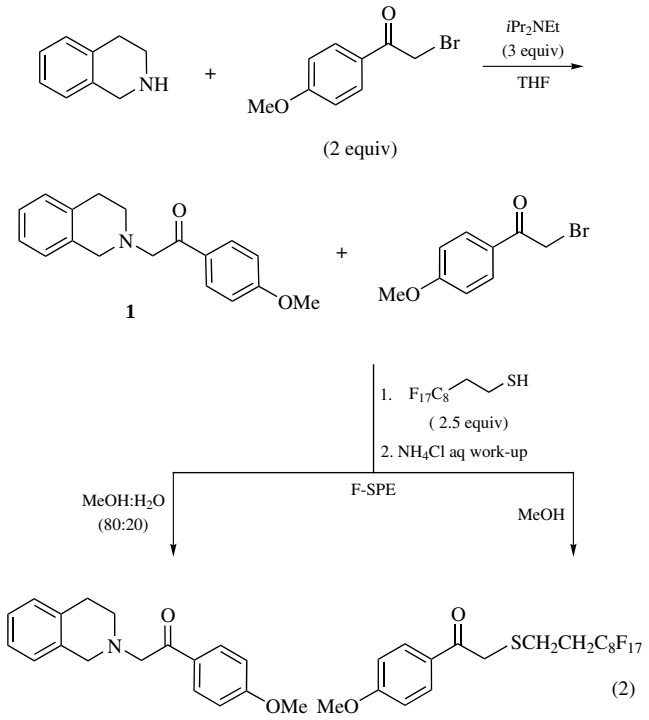
(1)

Purity: vacuum distillation (bp 82 °C/12 mm Hg).

Handling, Storage, and Precaution: fluorous thiol can be stored in a brown glass bottle under N_2 at room temperature for several months.

Applications as Nucleophilic Scavenger. The fluorous thiol can be used as a solution-phase scavenger to remove excess electrophiles.[1] The scavenged species and unreacted fluorous thiol can be separated from the product by solid-phase extraction over a Fluoro*Flash*™ (F-SPE) cartridge charged with fluorous silica gel.[2] A typical F-SPE procedure is as follows: the crude reaction mixture containing the fluorous and non-fluorous compounds is loaded onto a Fluoro*Flash*™ cartridge. It is then eluted with 80:20 MeOH:H_2O. The non-fluorous compound elutes out while the fluorous material is retained. A second elution with a fluorophilic solvent, such as MeOH, washes out the fluorous compounds. An example of using fluorous thiol to remove α-bromoketones in the synthesis of tertiary amines is shown in eq 2.[3] An excess amount of α-bromoketone (2.0 equiv) is used to consume the tetrahydroisoquinoline. The thiol scavenger (2.5 equiv) is then added

to the reaction mixture to quench the unreacted bromide. After an aqueous work-up to remove the DIPEA, the mixture is purified by F-SPE. Product **1** is collected from the MeOH–H_2O fraction, while scavenged species **2** and unreacted thiol scavenger are in the MeOH fraction.

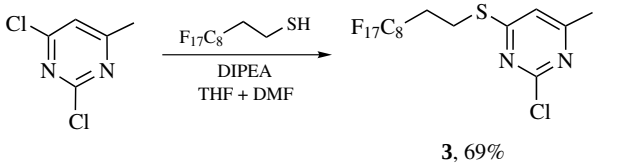


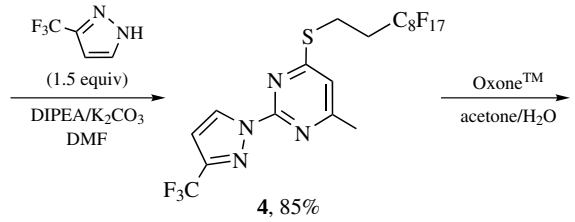
1, 93% (89% pure) **2**

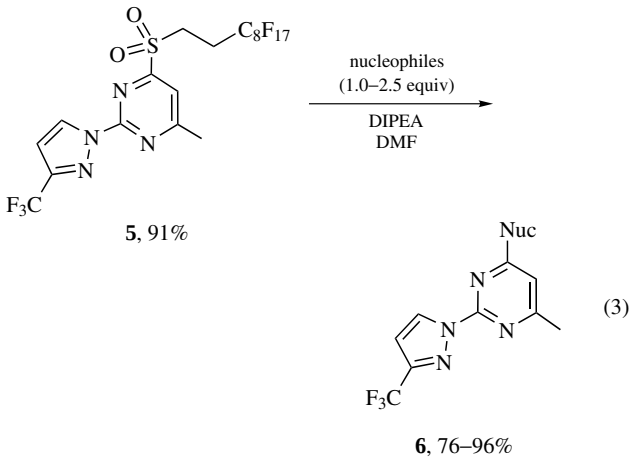
Fluorous scavenging is carried out under homogeneous solution-phase conditions and is advantageous over polymer-bound scavenging. The quenching process is fast and does not require a large excess of scavengers.[3]

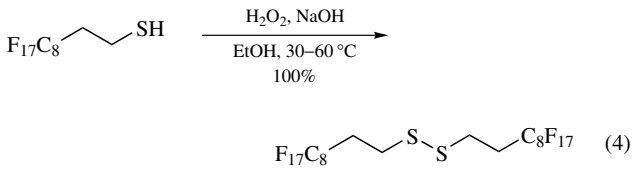
Use as Tag for Substituted Heterocycles. The fluorous thiol has been used as a phase tag to facilitate purification in the synthesis of disubstituted pyrimidines (eq 3).[4] Using a 'catch and release' strategy, the fluorous thiol is first attached to 2,4-dichloro-6-methylpyrimidine. Tagged pyrimidine **3** is then reacted with 3-trifluoromethylpyrazole to give **4**. After the fluorous tag is activated by oxidation with Oxone™, it is displaced by nucleophiles such as amines and thiols to give a variety of disubstituted pyrimidines. In this multi-step synthesis, the intermediates and the final product are purified by F-SPE. The fluorous intermediates are collected in the second fraction eluted with MeOH, while the final product is collected in the first fraction eluted with 80:20 MeOH:H_2O.

Use in Radical Reactions. Thiols are good sources for alkylthio radicals under oxidative conditions. The fluorous disulfide can be prepared from the thiol in excellent yield using 1.3 equiv of H_2O_2 and a catalytic amount of NaOH (1–2 mol %) (eq 4).[5] After the reaction is complete, the clear reaction mixture is separated into two layers, from which pure crystalline fluorous disulfide is filtered off.

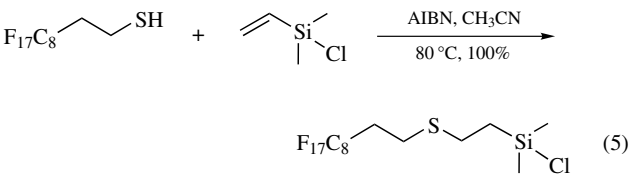






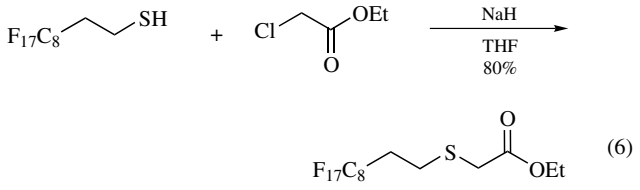


Another example of a radical reaction involves the addition of alkylthio radicals to alkenes using AIBN as a radical initiator. Equation 5 demonstrates the addition of fluorous thiol to vinyl silyl chloride to form fluorous functionalized silyl chloride in quantitative yield without forming polyaddition by-products.[6]

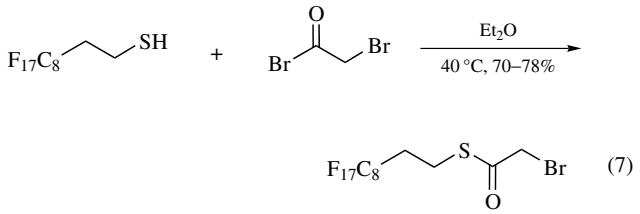


***S*-Alkylation/Acylation Reactions.** Similar to non-fluorous thiols, fluorous thiols can be alkylated or acylated by appropriate halides or acid halides to form sulfides[7] or thioesters[8] (eqs 6 and 7).

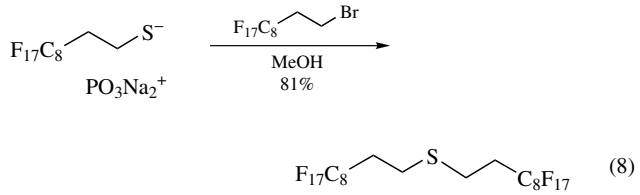
Formation of a bis-fluorous sulfide is accomplished by the alkylation of a fluorous thiol phosphate salt with a fluorous alkyl bromide (eq 8).[9] The salt is prepared from the fluorous thiol to avoid the oxidative dimerization of the thiol to form the disulfide.



(6)



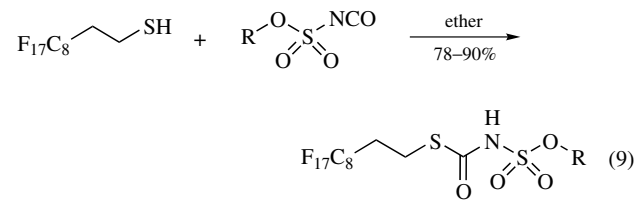
(7)



(8)

The fluorous thiol can also be reacted with CH_2Cl_2 in the presence of a base and a phase transfer catalyst to prepare bis-fluorous thiolacetal.[10]

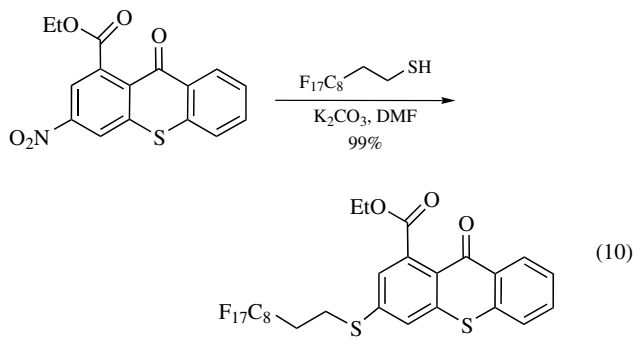
Other Nucleophilic Reactions. Fluorous thiol can react with alkoxysulfonyl or aryloxysulfonyl isocyanates to give the corresponding sulfonyl thiocarbamates under mild reaction conditions (eq 9).[11]



(9)

R = 2,4,6-trimethylphenyl, 4-nitrophenyl, 4-chlorophenyl, 2,2,2-trichloroethyl, 4-fluorophenyl, phenyl, 4-methylphenyl

Another example of a nucleophilic reaction is presented in eq 10, where the 3-nitro group of thioxanthone is substituted with fluorous thiol in the presence of K_2CO_3 to give the fluorous substituted thioxanthone.[12]



(10)

Related Reagents. 1*H*,1*H*,2*H*,2*H*-Perfluorooctanethiol; *S*-(1*H*,1*H*,2*H*,2*H*-Perfluorodecyl)thioacetate; 1*H*,1*H*,2*H*,2*H*-Perfluorodecyl Iodide; 1*H*,1*H*,2*H*,2*H*-Perfluorodecanesulfonic acid.

1. (a) Zhang, W., *Tetrahedron* **2003**, *59*, 4475. (b) Curran, D. P., *Angew. Chem., Int. Ed.* **1998**, *37*, 1175. (c) Curran, D. P. In *Stimulating Concepts in Chemistry*; Stoddard, F.; Reinhoudt, D.; Shibasaki, M., Eds.; Wiley-VCH: New York, 2000, p 25.
2. Curran, D. P., *Synlett* **2001**, 1488.
3. Zhang, W.; Curran, D. P.; Chen, C. H.-T., *Tetrahedron* **2002**, *58*, 3871.
4. Zhang, W., *Org. Lett.* **2003**, *5*, 1011.
5. Brace, N. O., *J. Fluorine Chem.* **2000**, *105*, 11.
6. Boutevin, B.; Pietrasanta, Y.; Sarraf, L., *J. Fluorine Chem.* **1986**, *31*, 425.
7. Dieng, S.; Bertaina, B.; Cambon, A., *J. Fluorine Chem.* **1985**, *28*, 425.
8. Sismondi, A.; Abenin, P.; Joncheray, L.; Cambon, A., *J. Fluorine Chem.* **1992**, *59*, 127.
9. Naud, C.; Calas, P.; Blancou, H.; Commeyras, A., *J. Fluorine Chem.* **2000**, *104*, 173.
10. Bertaina, B.; Rouvier, E.; Fayn, J.; Cambon, A., *J. Fluorine Chem.* **1994**, *66*, 287.
11. Beji, M.; Sbihi, H.; Baklouti, A.; Cambon, A., *J. Fluorine Chem.* **1999**, *99*, 17.
12. Fisher, W.; Kvita, V., *Helv. Chim Acta.* **1985**, *68*, 854.

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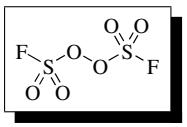
Fluorous Technologies, Inc., Pittsburgh, PA, USA

Peroxydisulfuryl Difluoride[1]



[13709-32-5] $F_2O_6S_2$ (MW 198.14)
InChI = 1/F2O6S2/c1-9(3,4)7-8-10(2,5)6
InChIKey = CTHHBLWYPDKYFP-UHFFFAOYAS

(fluorosulfating agent, capable of halogen[2–7] and hydrogen abstraction[2–9] reactions to give esters of fluorosulfuric acid; powerful oxidant[10,11])

Physical Data: bp 67.1 °C; mp −55.4 °C.[1,11,12]

Form Supplied in: colorless liquid with unpleasant odor.

Preparative Methods: can be obtained by the reaction of SO_3 with F_2 in the presence of AgF_2[11] or by electrolysis of fluorosulfuric acid.[12]

Handling, Storage, and Precautions: although the reagent appears to be stable and there are no reports of explosive properties, it should be handled with care. It can ignite organic materials upon contact. It is hydrolyzed by water to give oxygen and fluorosulfuric acid.[12] Use in a fume hood.

Synthesis of Fluorosulfates. The chemical behavior of $F_2S_2O_6$ is determined by two features of its reactivity: (a) the ability to generate the radical species $\bullet OSO_2F$ in the reversible

dissociation reaction,[2,13] and (b) the high oxidation ability[10,11] and, in particular, the generation of high-valent species containing two fluorosulfate groups.[1] The reagent (**1**) smoothly substitutes halogen atoms (Cl, Br, I) for fluorosulfate groups, probably via transient formation of hypervalent species of type (**2**) (eq 1).[3]

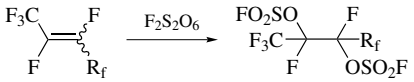
$$\underset{\textbf{(1)}}{RX + FSO_2OOSO_2F} \longrightarrow \underset{\textbf{(2)}}{\left[RX(OSO_2F)_2\right]} \longrightarrow ROSO_2F \quad (1)$$

For example, methyl chloride or bromide reacts with $F_2S_2O_6$ at −25 °C to give methyl fluorosulfate.[2] The reaction is applicable to fluorochlorocarbons (eq 2).[4]

$$CF_2ClCFCl_2 \xrightarrow{F_2S_2O_6} CF_2ClCFClOSO_2F \quad (2)$$

In the case of perfluoroalkyl iodides the relatively stable hypervalent iodine derivatives of type $R_fI(OSO_2F)_2$ can be isolated; they are also readily transformed into the corresponding fluorosulfates R_fOSO_2F.[5–7]

Perfluoroalkenes react with (**1**) to give *vic*-difluorosulfates,.[14–17] e.g. eq 3.[15]

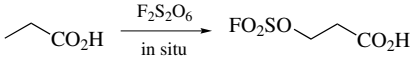


(3)

C_6F_6 also gives a 1,4-addition product and then 1,2,3,4- and 1,2,3,4,5,6-addition products.[18]

Hydrogen Abstraction. Reactions of (**1**) with a variety of organic compounds such as amines, alcohols, thiols, aromatics, and even saturated hydrocarbons, proceed by hydrogen abstraction and addition of an OSO_2F moiety (R–H → $ROSO_2F$).[1,2,8,9,19,20] For example, methane gives a mixture of methyl fluorosulfate and methylene difluorosulfate.[20] Methyl fluorosulfate also gives methylene difluorosulfate in reaction with (**1**)[2] Hexafluoropropane[8] and propionic acid[20] react in accordance with eqs 4 and 5.

$$(CF_3)_2CH_2 \xrightarrow{F_2S_2O_6} (CF_3)_2CHOSO_2F \quad (4)$$



(5)

Hexafluoroacetone imine also reacts with substitution of the imine hydrogen atom (eq 6).[19]

$$(CF_3)_2C{=}NH \xrightarrow{F_2S_2O_6} (CF_3)_2C{=}NOSO_2F + \underset{FO_2SO}{\overset{}{(CF_3)_2C}}-N{=}N-\underset{OSO_2F}{\overset{}{C(CF_3)_2}} \quad (6)$$

Benzene gives phenyl fluorosulfate[1] and nitrobenzene gives *m*-nitrophenyl fluorosulfate[21], respectively, in reaction with (**1**).

Oxidation. Peroxide (**1**) is a powerful oxidant and can be used for the oxidation of noble metals (Ag, Au, Re, Pt, Os, Rh) to the salts of fluorosulfuric acid.[10,22] For example, the oxidation of metallic silver by $F_2S_2O_6$ in the presence of $HOSO_2F$ gives $Ag(SO_3F)_2$.[22] Oxidation of organic compounds can produce radicals. For example, the trimer (**3**) of perfluoropropylene reacts with (**1**) to give stable radical (**4**), isolated in analytically pure form (eq 7).[23]

$$\underset{\textbf{(3)}}{[(CF_3)_2CF]_2C{=}CFCF_3} \xrightarrow{F_2S_2O_6} \underset{\textbf{(4)}}{[(CF_3)_2CF]_2\dot{C}-\underset{OSO_2F}{\overset{}{CFCF_3}}} \quad (7)$$

Dimethyl ether reacts with (**1**) to give dimethoxyethane as the sole product, presumably via selective dimerization of transient methoxymethyl radicals (eq 8).[24]

$$\underset{\textbf{(1)}}{2\,Me_2O + FSO_2OOSO_2F} \xrightarrow{FSO_3H} MeOCH_2CH_2OMe + 2\,FSO_3H \quad (8)$$

Carbon monooxide is oxidized by (**1**) to CO_2.[3] Nitroso groups in perfluoronitrosoalkanes are either oxidized to nitro groups or undergo substitution by an OSO_2F group.[25]

1. Fokin, A. V.; Studnev, Yu. N.; Kuznetzova, L. D.; Krotovich, I. N., *Usp. Khim.* **1982**, *51*, 1258 (*Chem. Abstr.* **1982**, *97*, 181 258m).
2. Kirchmeier, R. L.; Shreeve, J. M., *Inorg. Chem.* **1973**, *12*, 2886.
3. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Kuznetzova, L. D.; Verenikin, O. V.; Krotovich, I. N., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 2422 (*Chem. Abstr.* **1977**, *86*, 89 108n).
4. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Matveenko, V. I., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 715 (*Chem. Abstr.* **1985**, *103*, 70 907v).
5. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Tatarinov, A. S.; Pasevina, K. I., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 1669 (*Chem. Abstr.* **1986**, *104*, 185 943s).
6. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Potarina, T. M.; Kuznetzova, L. D., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 2641 (*Chem. Abstr.* **1981**, *94*, 191 609d).
7. Schack, C. J.; Christe, K. O., *J. Fluorine Chem.* **1980**, *16*, 63.
8. Fokin, A. V.; Rapkin, A. I.; Matveenko, V. I.; Zakharov, V. Yu.; Studnev, Yu. N., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1986**, 252 (*Chem. Abstr.* **1987**, *106*, 32 320c).
9. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Kuznetzova, L. D.; Komarov, V. A., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 489 (*Chem. Abstr.* **1976**, *85*, 20 539r).
10. (a) Willner, H.; Aubke, F., *Inorg. Chem.* **1990**, *29*, 2195. (b) Mallela, P.; Aubke, F., *Inorg. Chem.* **1985**, *24*, 2969. (c) Lee, K. C.; Aubke, F., *Inorg. Chem.* **1984**, *23*, 2124. (d) Leung, P. C.; Wong, G. B.; Aubke, F., *J. Fluorine Chem.* **1987**, *35*, 607. (e) Cicha, W. V.; Herring, F. G.; Aubke, F., *Can. J. Chem.* **1990**, *68*, 102.
11. (a) Dudley, F. B.; Cady, G. H., *J. Am. Chem. Soc.* **1957**, *79*, 513. (b) Shreeve, J. M.; Cady, G. H., *Inorg. Synth.* **1963**, *7*, 124.
12. Dudley, F. B., *J. Chem. Soc.* **1963**, 3407.
13. Zimmerman, E. C.; Ross, J., *J. Chem. Phys.* **1984**, *80*, 720.
14. Shreeve, J. M.; Cady, G. H., *J. Am. Chem. Soc.* **1961**, *83*, 4521.
15. Kurykin, M. A.; Krotovich, I. N.; Studnev, Yu. N.; German, L. S.; Fokin, A. V., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 1861 (*Chem. Abstr.* **1982**, *97*, 215 441h).
16. Kurykin, M. A.; German, L. S.; Studnev, Yu. N.; Fokin, A. V., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 1679 (*Chem. Abstr.* **1980**, *93*, 238 771x).
17. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Krotovich, I. N.; Verenikin, O. V., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 1094 (*Chem. Abstr.* **1985**, *103*, 214 819t).
18. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Krotovich, I. N.; Kuznetzova, L. D.; Komarov, V. A., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 946 (*Chem. Abstr.* **1976**, *85*, 62 723b).

19. Fokin, A. V.; Rapkin, A. I.; Krotovich, I. N., *Zh. Org. Khim.* **1986**, *21*, 2225 (*Chem. Abstr.* **1986**, *105*, 171 777z).
20. Coleman, J. P.; Pletcher, D., *Tetrahedron Lett.* **1974**, 147.
21. Fokin, A. V.; Nikolaeva, A. D.; Studnev, Yu. N.; Proshin, N. A.; Leonov, A. G., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, 2638 (*Chem. Abstr.* **1982**, *96*, 85 161h).
22. Leung, P. C.; Aubke, F., *Inorg. Chem.* **1978**, *17*, 1765.
23. Cherstkov, V. F.; Avetisjan, E. A.; Tumanskyi, B. L.; Sterlin, S. R.; Bubnov, N. N.; German, L. S., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 2450 (*Chem. Abstr.* **1991**, *114*, 42 026r).
24. Choukroun, H.; Brunel, D.; Germain, A., *J. Chem. Soc., Chem. Commun.* **1986**, 6.
25. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Krotovich, I. N.; Chilikin, V. G.; Verenikin, O. V., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 832 (*Chem. Abstr.* **1984**, *101*, 130 177c).

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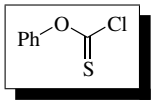
Phenyl Chlorothionocarbonate

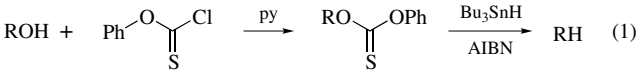


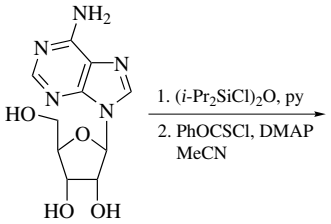
[1005-56-7] C_7H_5ClOS (MW 172.64)
InChI = 1/C7H5ClOS/c8-7(10)9-6-4-2-1-3-5-6/h1-5H
InChIKey = KOSYAAIZOGNATQ-UHFFFAOYAQ

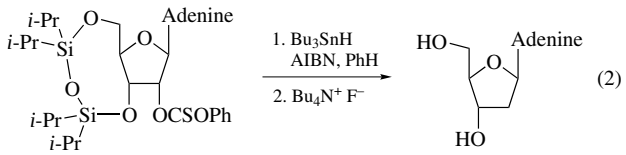
(forms thionocarbonate ester derivatives of alcohols which can be deoxygenated with tin hydride reagents;[1–5] converts ribonucleosides to 2′-deoxynucleosides;[2] provides allylic thionocarbonates which undergo [3,3]-sigmatropic shifts;[6–9] provides precursors for radical bond-forming reactions;[10,11] reagent for thioacylation[12–16])

Physical Data: bp 81–83 °C/6 mmHg; fp 81 °C; *d* 1.248 g cm^{-3}.
Solubility: sol chloroform, THF.
Form Supplied in: colorless liquid.
Handling, Storage, and Precautions: corrosive; moisture sensitive; should be stored in airtight containers which exclude moisture; incompatible with alcohol solvents.

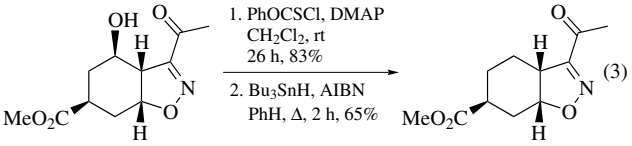
Deoxygenation of Secondary Alcohols. Reaction of secondary alcohols with the reagent in the presence of pyridine or 4-dimethylaminopyridine (DMAP) provides thiocarbonate ester derivatives which can be reduced to alkanes using tributylstannane (eq 1).[1] The advantage of this method is the ability to deoxygenate alcohols via radical intermediates and thereby avoid problems associated with ionic reaction conditions (i.e. carbonium ion rearrangements, reduction of other functional groups). This method is particularly useful for the conversion of ribonucleosides to 2′-deoxynucleosides. For example, adenosine can be converted to 2′-deoxyadenosine in 78% overall yield by initial protection of the 3′- and 5′-hydroxyl groups as a cyclic disiloxane, thiocarbonylation, reductive cleavage, and then final deprotection using a fluoride source (eq 2).[2] Treatment of 2′-bromo-3′-phenoxythiocarbonyl nucleosides with tributyltin hydride affords 2′,3′-didehydro-2′,3′-dideoxy nucleosides via radical β-elimination.[3]







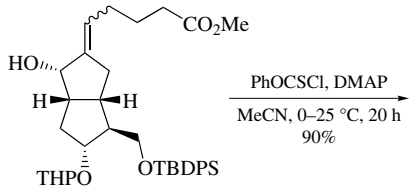
Synthetic intermediates can be selectively deoxygenated without reduction of other functional groups such as esters, ketones, and oxime ethers (eq 3),[4] as well as epoxides, acetate esters, and alkenes.[5]

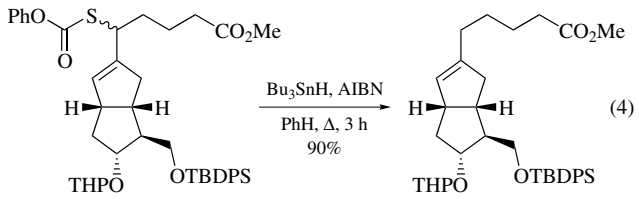


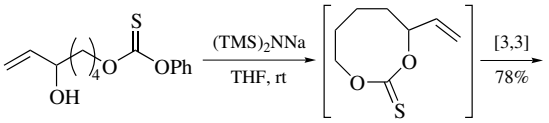
Sigmatropic Rearrangements of Allylic Thionocarbonates. The reaction of allyl alcohols with aryl chlorothionocarbonates affords *S*-allyl aryl thiocarbonates by [3,3]-sigmatropic rearrangement via the intermediate thionocarbonate esters.[6–9] For example, treatment of 2-methyl-1-penten-3-ol with the reagent in pyridine at −20 °C affords phenyl 2-methyl-2-pentenyl thionocarbonate in 67% yield (*E*:*Z* = 96.5:3.5).[7] This type of rearrangement, coupled with tin hydride mediated reduction of the phenyl thiocarbonate ester product, was used as a key step in the synthesis of isocarbacyclin (eq 4).[8] Rearrangement of cyclic thionocarbonates contained in eight-membered rings or smaller provides two-atom ring enlarged thiocarbonates having (*Z*) double bond geometry (eq 5).[9] Depending on the system, the cyclic thiocarbonates are obtained by either treatment of the diol monothionocarbonate with base or by reaction of the diol with 1,1′-thiocarbonyldi-2,2′-pyridone. Cyclic thionocarbonates of ring size nine or larger afford ring expanded products with exclusive (*E*) double bond geometry in modest yields.

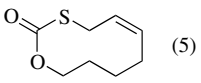
Radical Coupling and Cyclization Reactions. Phenyl thionocarbonate esters derived from alcohols serve as efficient precursors for the generation of radical intermediates which can be used for the formation of new carbon–carbon bonds. For example, a 4-thionocarbonate ester derived from L-lyxose undergoes a stereoselective allylation upon photolysis in toluene in the presence of 2.0 equiv of allyltributylstannane (eq 6).[10] Photochemical initiation is preferable to chemical initiation using azobisisobutyronitrile which results in the formation of side products at the

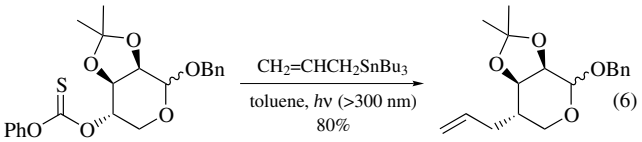
expense of the desired product. The allylation product was used further in a total synthesis of pseudomic acid C.



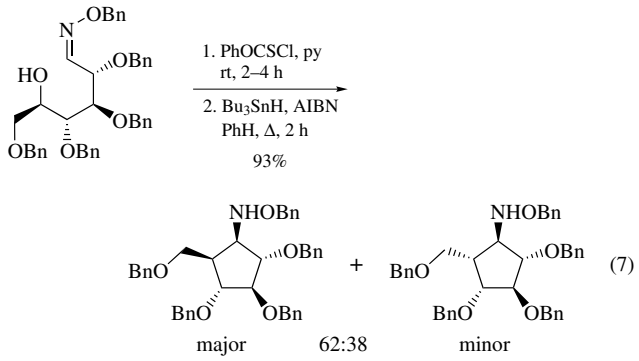




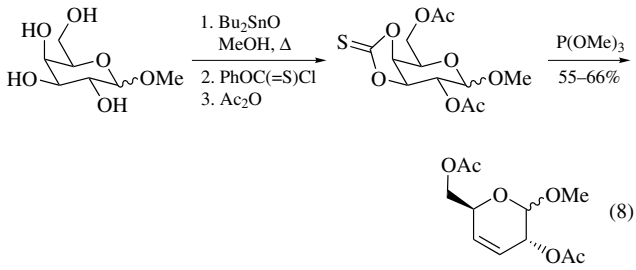




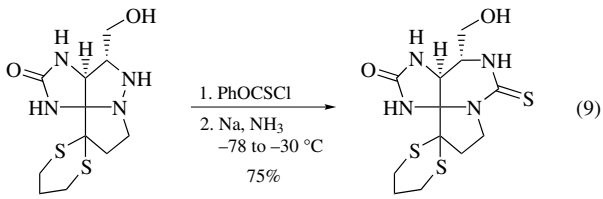
Oxime ethers derived from hydroxy aldehydes, upon conversion to their phenyl thionocarbonate esters, undergo radical cyclizations resulting in the formation of carbocycles.[11] For example, an oxime ether obtained from D-glucose is converted into its phenyl thionocarbonate ester at C-5 and, upon heating in benzene in the presence of tributyltin hydride, affords cyclopentanes in 93% yield as a 62:38 mixture of two diastereomers (eq 7). In general, only low to modest stereoselectivity between the newly formed stereocenters is observed in a number of substrates examined.



Thioacylation Reagent. The regioselective thioacylation of unprotected carbohydrates via the agency of dibutyltin oxide and the reagent has been investigated.[12] Glycopyranosides having a *cis*-diol arrangement, e.g. galactose, form cyclic thiocarbonates which can be either converted into dihydropyranosides using the Corey elimination procedure or deoxygenated to a mixture of 3- and 4-deoxyglycopyranosides (eq 8). Methyl D-glucopyranoside is monothioacylated with the regioselectivity dependent upon the configuration at the anomeric carbon; the α-epimer gives 83% of 2-thionocarbonate and the β-epimer gives 85% of 6-thionocarbonate. Further treatment with tributyltin hydride affords the corresponding deoxyglucose derivatives in high yield.

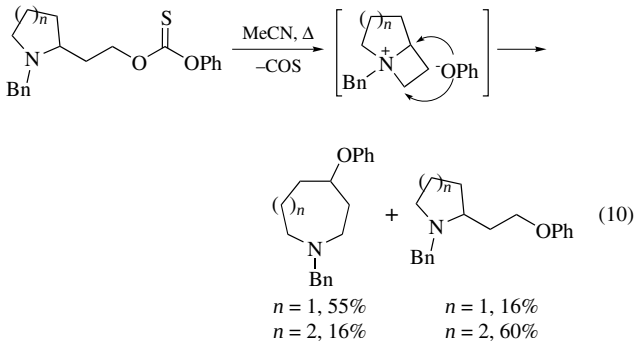


In a key step leading to a synthesis of saxitoxin, radical fragmentation of a pyrazolidine ring followed by intramolecular thioacylation afforded the ring expanded tetrahydropyrimidine intermediate (eq 9).[13] The thionocarbamate activation of the pyrazolidine *N*-H was found to be necessary to effect the desired transformation.



The intramolecular thioacylation of an ester enolate was used for the synthesis of 2-alkylthiopenem carboxylic acid derivatives.[14] Sequential acylations have led to the synthesis of zwitterionic pyrazole-5-thiones from acyclic precursors,[15] whereas 2-ethoxyoxazolidines react with the reagent to afford the products of *N*-acylation.[16]

Heating of *O*-phenyl thionocarbonates of pyrrolidine and piperidine-2-ethanols in acetonitrile gives a ring expanded azepine or an octahydroazocine accompanied by the pyrrolidine and piperidine *O*-phenyl ethers (eq 10).[17] These products arise via the internal expulsion of carbonyl sulfide, leading to formation of an azetidinium intermediate followed by nucleophilic ring opening with phenoxide ion.



Related Reagents. Carbon Disulfide; *p*-Tolyl Chlorothionocarbonate.

1. Barton, D. H. R.; Subramanian, R., *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.
2. Robins, M. J.; Wilson, J. S., *J. Am. Chem. Soc.* **1981**, *103*, 932; Robins, M. J.; Wilson, J. S.; Hansske, F., *J. Am. Chem. Soc.* **1983**, *105*, 4059.
3. Serafinowski, P., *Synthesis* **1990**, 411.
4. Martin, S. F.; Dappen, M. S.; Dupre, B.; Murphy, C. J., *J. Org. Chem.* **1987**, *52*, 3706.
5. Schuda, P. F.; Potlock, S. J.; Wannemacher, Jr., R. W., *J. Nat. Prod.* **1984**, *47*, 514.
6. Garmaise, D. L.; Uchiyama, A.; McKay, A. F., *J. Org. Chem.* **1962**, *27*, 4509.
7. Faulkner, D. J.; Petersen, M. R., *J. Am. Chem. Soc.* **1973**, *95*, 553.
8. Torisawa, Y.; Okabe, H.; Ikegami, S., *J. Chem. Soc., Chem. Commun.* **1984**, 1602.
9. Harusawa, S.; Osaki, H.; Kurokawa, T.; Fujii, H.; Yoneda, R.; Kurihara, T., *Chem. Pharm. Bull.* **1991**, *39*, 1659.
10. Keck, G. E.; Kachensky, D. F.; Enholm, E. J., *J. Org. Chem.* **1985**, *50*, 4317.
11. Bartlett, P. A.; McLaren, K. L.; Ting, P. C., *J. Am. Chem. Soc.* **1988**, *110*, 1633.
12. Haque, M. E.; Kikuchi, T.; Kanemitsu, K.; Tsuda, Y., *Chem. Pharm. Bull.* **1987**, *35*, 1016.
13. Jacobi, P. A.; Martinelli, M. J.; Polanc, S., *J. Am. Chem. Soc.* **1984**, *106*, 5594.
14. Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkering, R. R.; Wildonger, K. J.; Ratcliffe, R. W.: Christensen, B. G., *Tetrahedron* **1983**, *39*, 2505.
15. Grohe, K.; Heitzer, H.; Wendisch, D., *Liebigs Ann. Chem.* **1982**, 1602.
16. Widera, R.; Muehlstaedt, M., *J. Prakt. Chem.* **1982**, *324*, 1005.
17. Sakanoue, S.; Harusawa, S.; Yamazaki, N.; Yoneda, R.; Kurihara, T., *Chem. Pharm. Bull.* **1990**, *38*, 2981.

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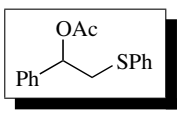
1-Phenyl-2-(phenylsulfanyl)ethyl Acetate



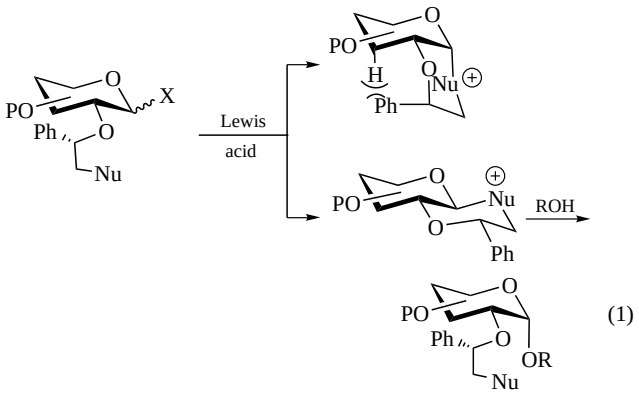
(*s*)
[865860-14-6]
(*rac*)
InChI = 1/C16H16OS/c1-13(17)16(14-8-4-2-5-9-14)12-18-15-10-6-3-7-11-15/h2-11,16H,12H2,1H3/t16-/m0/s1
InChIKey = DJQIXAYZMAYRBE-INIZCTEOBZ
[16162-49-5] $C_{16}H_{15}OS$ (MW 271.3)
InChI = 1/C16H16O2S/c1-13(17)18-16(14-8-4-2-5-9-14)12-19-15-10-6-3-7-11-15/h2-11,16H,12H2,1H3
InChIKey = VOMPWOVNVXDARN-UHFFFAOYAG

(reagent used as chiral auxiliary in stereoselective glycosylation reactions[1])

Alternate Names: α-[(phenylthio)methyl]benzenemethanol acetate; 1-phenyl-2-(phenylthio)ethyl acetate.

Preparative Method: the title compound with *S*-configuration can be made from (*S*)-mandelic acid following a four-step reaction sequence:[1] reduction ($LiAlH_4$), selective tosylation ($TsCl/Bu_2SnO/Et_3N$), displacement (NaSPh), and acetylation (Ac_2O/pyridine). The racemic isomer can be prepared by electrophilic addition to styrene.[2]

It is the general experience of carbohydrate chemists that the formation of 1,2-*cis* glycosidic linkages[3] (α-glucosides, α-galactosides, and β-mannosides) is more demanding than that of 1,2-*trans* glycosides (β-glucosides, β-galactosides, and α-mannosides). Neighboring group assistance of substituents (Ac, Bz, Piv) at the O-2 position is sufficient to promote stereoselective 1,2-*trans* glycosylation. Although glycosylation of donors bearing nonparticipating group (Bn) at the O-2 position favors 1,2-*cis* glycoside formation, it usually leads to a mixture of α- and β-glycosides, which limits the use of such methods in one-pot multistep glycosylations[4] and in polymer-supported synthesis.[5] Recently, Boons described a novel approach to 1,2-*cis* glycosides making use of participation by a chiral auxiliary at the O-2 position.[1,6] Upon formation of an oxonium ion, participation of the chiral auxiliary with *S*-configuration was expected to result only in the formation of the *trans*-decalinoid intermediate due to unfavorable steric interactions in the *cis*-decalinoid isomer. Subsequent opening of the *trans*-decalinoid intermediate would furnish a 1,2-*cis* glycoside (eq 1).[1]

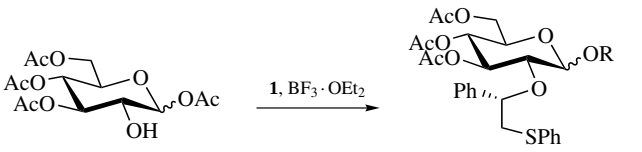


(1)

Boons explored the application of ethyl mandelate as first-generation chiral auxiliary in 1,2-*cis* glycosylation reaction.[6] However, it was shown that the desired 1,2-*cis* glycoside was accompanied by a small amount of the undesired anomer. The use of an auxiliary based on the 1-phenyl-2-phenylthioethyl group, however, resulted in excellent selectivities for the desired 1,2-*cis* glycosides.[1]

The (1*S*)-phenyl-2-(phenylsulfanyl) moiety could be installed easily by the treatment of a sugar alcohol with 1-phenyl-2-phenylthioethyl acetate **1** in the presence of $BF_3 \cdot OEt_2$ with overall retention of configuration (eq 2).

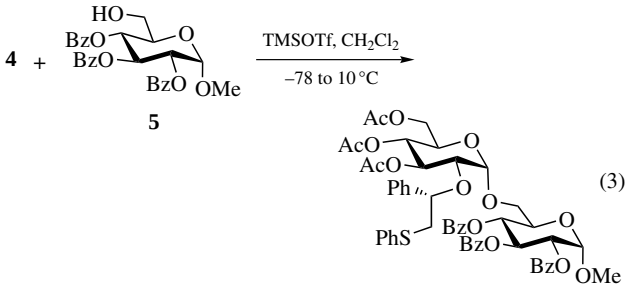
As expected, trichloroacetimidate **4** reacted with primary and secondary alcohols, in the presence of TMSOTf and DTBMP, to produce 1,2-*cis* disaccharides in high yield as single stereoisomers (eqs 3 and 4).[1]



(2)

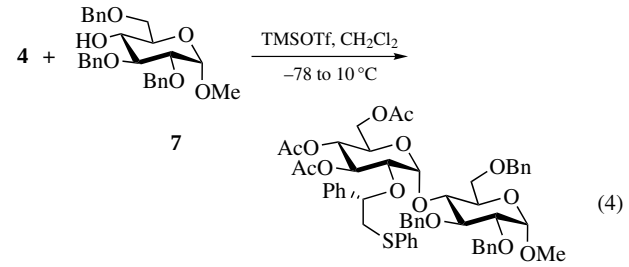
$H_2NNH_2 \cdot HOAc$ (83%) → **2**: R = OAc → **3**: R = OH

Cl_3CCN/DBU (95%) → **4**: R = $C(NH)CCl_3$



(3)

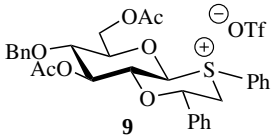
6 α only (94%)



(4)

8 α only (83%)

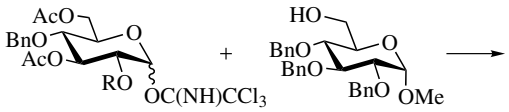
The *trans*-decalinoid intermediate **9** has been characterized by ^1H, ^1H TOCSY, and HMBC NMR experiments.[1]



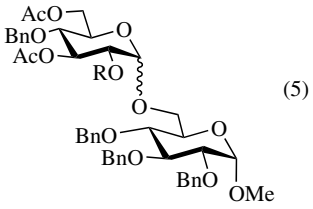
9

Screening of various additives and auxiliaries indicated that an equatorially oriented (1*S*)-phenyl substituent and *trans*-decalinoid intermediate formation were important features for controlling the anomeric selectivity (eq 5).[1] In particular, the use of the corresponding (*R*)-enantiomer of the auxiliary resulted in a very significant erosion of selectivity.

To demonstrate the application of the above methodologies in carbohydrate synthesis, trisaccharide **18** was prepared in a one-pot multistep manner (eq 6).[1] It is worth noting that the (1*S*)-phenyl-2-(phenylsulfanyl) moiety is able to survive NIS-promoted glycosylation reactions and can be transferred into the corresponding acetate by treatment with $BF_3 \cdot OEt_2/Ac_2O$ without detriment to the glycosidic linkages.



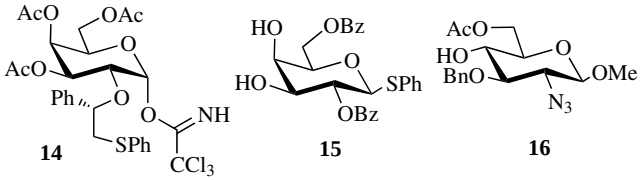
10: R = Bn
11: R = $(CH_2)_2SPh$
12: R = (*R*)-CH(Ph)CH_2SPh
13: R = (*S*)-CH(Ph)CH_2SPh



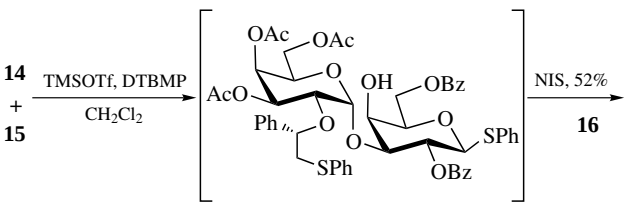
(5)

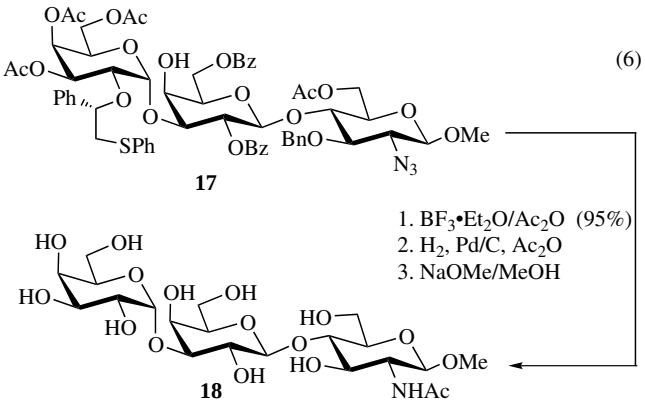
10a: R = Bn
a. TMSOTf, CH_2Cl_2, α/β = 3/1 (94%)
b. TMSOTf, CH_2Cl_2, PhSEt, α/β = 6/1 (92%)

11a: R = $(CH_2)_2SPh$, α/β = 8/1 (86%)
12a: R = (*R*)-CH(Ph)CH_2SPh, α/β = 1/1 (88%)
13a: R = (*S*)-CH(Ph)CH_2SPh, α only, (95%)



14 **15** **16**





(6)

17

18

Related Reagents. (*S*)/(*R*)-Ethyl mandelate;[6] Thiophene;[7] Picolyl bromide.[8]

1. Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J., *J. Am. Chem. Soc.* **2005**, *127*, 12090.

2. (a) Mukaiyama, T.; Endo, T.; Ikenaga, S.; Osonoi, K., *J. Org. Chem.* **1968**, *33*, 2242. (b) Akai, S.; Takeda, Y.; Lio, K.; Takahashi, K.; Fukuda, N.; Kita, Y., *J. Org. Chem.* **1997**, *62*, 5526. (c) Taniguchi, N., *J. Org. Chem.* **2006**, *71*, 7874.
3. Demckenko, A. V., *Synlett* **2003**, 1225.
4. (a) Koeller, K. M.; Wong, C. H., *Chem. Rev.* **2000**, *100*, 4465. (b) Wang, Y.; Ye, X.-S.; Zhang, L.-H., *Org. Biomol. Chem.* **2007**, *5*, 2189.
5. Bufali, S.; Seeberger, P. H., *Org. React.* **2007**, *68*, 303.
6. (a) Kim, J.-H.; Yang, H.; Boons, G.-J., *Angew. Chem., Int. Ed.* **2005**, *44*, 947. (b) Kim, J.-H.; Yang, H.; Khot, V.; Whitefield, D.; Boons, G.-J., *Eur. J. Org. Chem.* **2006**, 5007.
7. Park, J.; Kawatkar, S.; Kim, J.-H.; Boons, G.-J., *Org. Lett.* **2007**, *9*, 1959.
8. Smoot, J. T.; Pornsuriyasak, P.; Demckenko, A. V., *Angew. Chem., Int. Ed.* **2005**, *44*, 7123.

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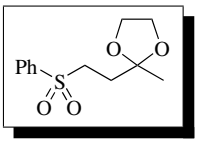
4-Phenylsulfonyl-2-butanone Ethylene Acetal



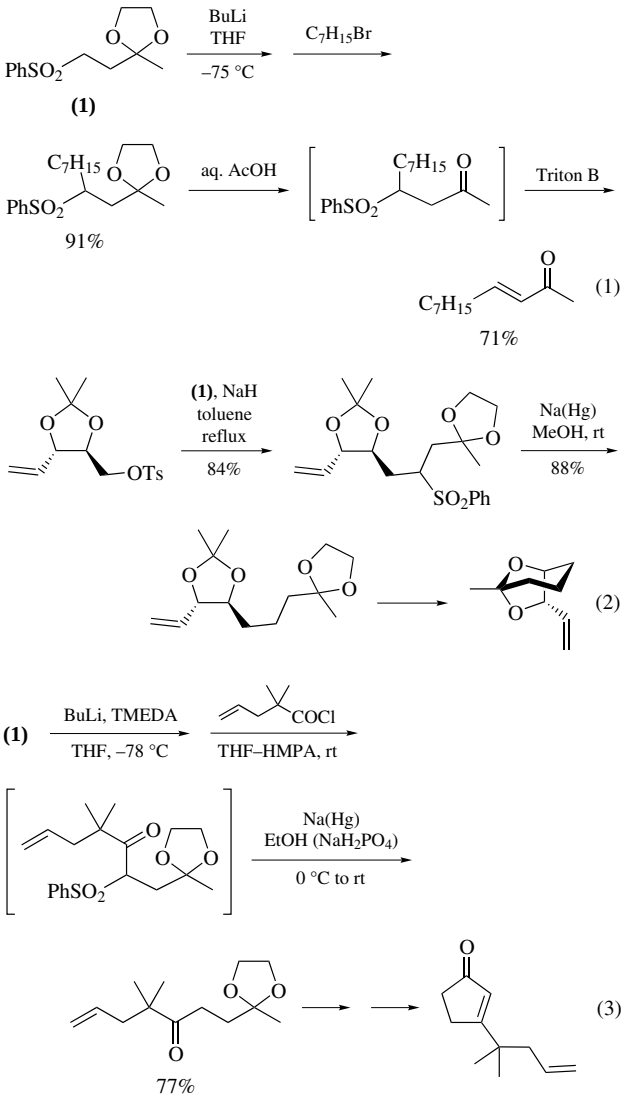
[56161-54-7] $C_{12}H_{16}O_4S$ (MW 256.35)
InChI = 1/C12H16O4S/c1-12(15-8-9-16-12)7-10-17(13,14)11-5-3-2-4-6-11/h2-6H,7-10H2,1H3
InChIKey = YVBGQPGMXFSZHS-UHFFFAOYAC

(a reagent for synthesizing various derivatives of 2-alkanones)

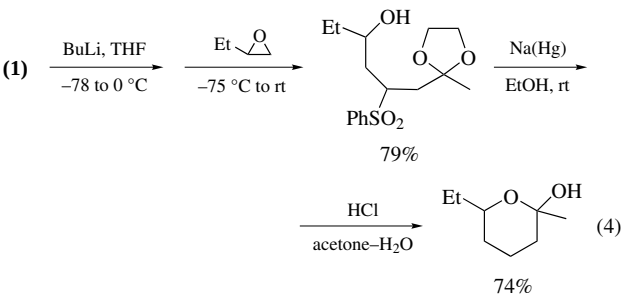
Alternate Name: PSB-EA.
Physical Data: colorless crystals; mp 33–34 °C or 41–42 °C.[1,2]
Preparative Method: by the Michael addition of benzenesulfinic acid to 3-buten-2-one followed by acetalization with ethylene glycol.[1,2]

Synthesis of 2-Alkanones and 3-Alken-2-one. Monoalkylation of 4-phenylsulfonyl-2-butanone ethylene acetal **1** takes place at the position α to the phenylsulfonyl group on successive treatment with butyllithium and then with an alkyl halide (or tosylate). Deprotection of the acetal group and subsequent elimination of the benzenesulfinic acid moiety with a base transforms the monoalkylation product to the corresponding 3-alken-2-one (eq 1).[1,3] A 2-alkanone is obtainable from the monoalkylation product by reductive desulfurization and subsequent acidic deprotection (eq 2).[2–5]

Alkane-2,5-dione Synthesis. On treatment with *n*-BuLi and an acyl chloride, (**1**) affords an α-acylated product, which easily undergoes reductive desulfurization with aluminum amalgam or sodium amalgam. Deprotection forms an alkane-2,5-dione (eq 3).[6,7]



Synthesis of 6-Hydroxy-2-alkanones. The lithio derivative of **1** reacts with a terminal epoxide to give a ring-opened product. Acidic deprotection of the product forms 6-hydroxy-2-alkanone which cyclizes to give a δ-lactol (eq 4).[8]



Related Reagents. 3-(Phenylsulfonyl)propanal Ethylene Acetal.

1. Kondo, K.; Tunemoto, D., *Tetrahedron Lett.* **1975**, 1007.
2. Wershofen, S.; Classen, A.; Scharf, H. D., *Liebigs Ann. Chem.* **1989**, 9.

3. Fürst, A.; Labler, L.; Meier, W., *Helv. Chim. Acta* **1982**, *65*, 1499.
4. Kato, T.; Takayanagi, H.; Uyehara, T.; Kitahara, Y., *Chem. Lett.* **1977**, 1009.
5. Wershofen, S.; Scharf, H. D., *Synthesis* **1988**, 854.
6. Kondo, K.; Tsunemoto, D., *Tetrahedron Lett.* **1975**, 1397.
7. Paquette, L. A.; Galemmo, R. A., Jr., Caille, J. C.; Valpey, R. S., *J. Org. Chem.* **1986**, *51*, 686.
8. Kondo, K.; Saito, E.; Tunemoto, D., *Tetrahedron Lett.* **1975**, 2275.

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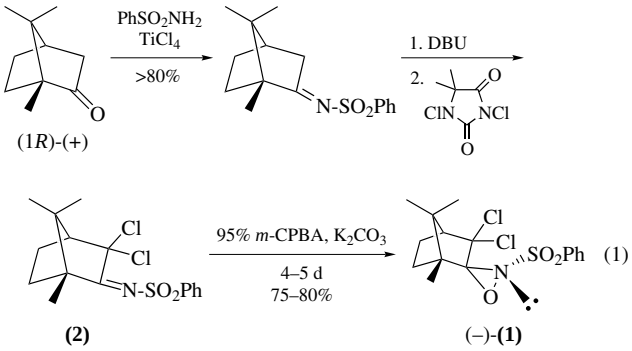
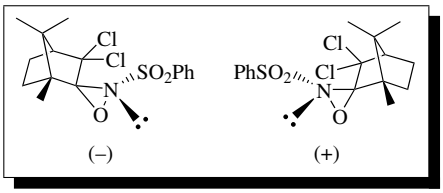


N-(Phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine[1]



(−)
[22270-28-4] $C_{16}H_{19}Cl_2NO_3S$ (MW 376.33)
InChI = 1/C16H19Cl2NO3S/c1-13(2)12-9-10-14(13,3)16(15(12, 17)18)19(22-16)23(20,21)11-7-5-4-6-8-11/h4-8,12H,9-10H2,1-3H3/t12-,14+,16?,19-/m0/s1
InChIKey = SKXAHVPODUVSJW-IDOUZKKGBR
(+)
[138874-52-9]
InChI = 1/C16H19Cl2NO3S/c1-13(2)12-9-10-14(13,3)16(15(12,17)18)19(22-16)23(20,21)11-7-5-4-6-8-11/h4-8,12H,9-10H2,1-3H3/t12-,14+,16?,19-/m1/s1
InChIKey = SKXAHVPODUVSJW-DDAVFFBNBO

(asymmetric oxidizing reagent for the enantioselective oxidation of sulfides to sulfoxides,[1] selenides to selenoxides,[2] and sulfenimines to sulfinimines[3])

Physical Data: mp 121–122 °C; (3′*S*,2*R*)-(−) $[\alpha]_D^{20}$ −159° (*c* 4.2, $CHCl_3$); (3′*R*,2*S*)-(+) $[\alpha]_D^{20}$ +157° (*c* 4.1, $CHCl_3$).

Solubility: insol H_2O; sol CH_2Cl_2, $CHCl_3$, THF, alcohols; sparingly sol CCl_4.

Form Supplied in: white solid.

Analysis of Reagent Purity: by mp and specific rotation determination.

Preparative Methods: the (−)-oxaziridine (**1**) is prepared from (1*R*)-(+)-camphor by condensation with benzenesulfonamide/$TiCl_4$ (eq 1). The chlorine atoms are introduced via the sulfonimine azaenolate by treatment with sodium hexamethyldisilazide and *N*-chlorosuccinimide or preferably with 1,8-diazabicyclo[5.4.0]undec-7-ene and 1,3-dichloro-5,5-dimethylhydantoin.[4,5] Although oxidation of the dichlorosulfonimine (**2**) requires >95% *m*-chloroperbenzoic acid and 4–5 days for completion, the oxidation can be carried out on a multigram scale (>60 g). Higher yields of (**1**) are obtained when (**2**) is dissolved in a minimum of the CH_2Cl_2 solvent. The antipode, (+)-(**1**), is similarly available from (1*S*)-(−)-camphor. In contrast to 2-(phenylsulfonyl)-3-phenyloxaziridine, this less reactive reagent does not epoxidize alkenes or oxidize amines to amine oxides.

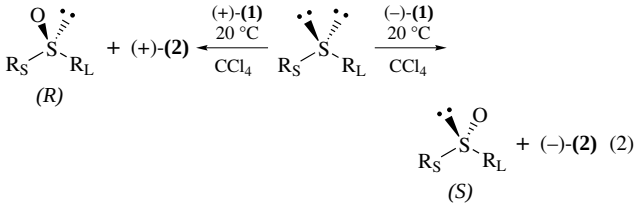
Purification: flash chromatography.

Handling, Storage, and Precautions: store at room temperature.

Asymmetric Oxidation of Sulfides to Sulfoxides. Enantiopure sulfoxides are important as auxiliaries in the asymmetric construction of C–C bonds.[6] The reaction of an organometallic reagent with a diastereomerically pure (−)-(1*R*,2*S*,5*R*)-menthyl (*S*)-*p*-toluenesulfinate, the Andersen synthesis, is the method most often employed for the preparation of nonracemic sulfoxides.[7,8] However, this methodology is limited in the synthesis of highly functionalized sulfoxides as well as certain dialkyl sulfoxides. Alternatively, enantiomerically enriched sulfoxides are available via the asymmetric oxidation of prochiral sulfides to sulfoxides using Kagan's modification of the Sharpless reagent, synthetically useful (>90% ee) only for aryl methyl sulfides (Ar–S–Me)[9] or the more general *N*-sulfonyloxaziridines (**1**).[1]

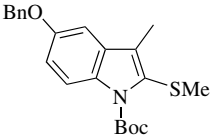
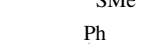
The asymmetric oxidation of sulfides to the sulfoxides by (−)-(**1**) is carried out at rt in nonpolar solvents (eq 2). Oxidations are generally complete within 1–6 h, although sulfides having electron-withdrawing or sterically demanding groups may require up to 48 h for completion. In these examples, heating to ca. 65 °C increases the rate of oxidation without significantly lowering the ee value. The sulfoxides and the sulfonimines (**2**) are isolated by TLC in >90% yield, with the latter being recycled. The highest enantioselectivities are observed for oxidations in low dielectric solvents such as CCl_4 and for those sulfides (R_L–S–R_S) where the difference in size of the R_L and R_S groups is large, e.g. R_L = aryl or *t*-butyl and R_S = CH_2R. Both enantiomeric sulfoxides are available by choice of the appropriate reagent because the configuration of the oxaziridine three-membered ring controls the absolute stereochemistry of the product, e.g. (−)-(**1**) gives (*S*)-sulfoxides while (+)-(**1**) gives (*R*)-sulfoxides (eq 2). The molecular recognition is predictable in terms of minimization of nonbonded steric interactions in the transition state. Examples are given in Table 1.[1,8c,10]

Asymmetric oxidation of 2,3-epoxy sulfides with (−)-(**1**), double stereodifferentiation, gives 2,3-epoxy sulfoxide diastereoisomers (eq 3).[11] Lower de values were observed for the other epoxy sulfide enantiomer. The modified Sharpless reagent gave better de values (5.1:1) with the methyl sulfides.

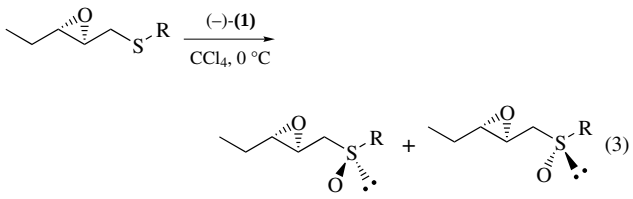


(2)

Table 1 Asymmetric oxidation of sulfides to sulfoxides[a] using (+)- and (−)-(**1**)[1]

Sulfide	Oxaziridine	% ee (config.)	Yield (%)	Time (h)
p-Tol–S–Me	(−)-(**1**)	>95 (*S*)	95	1
p-Tol–S–Bu	(−)-(**1**)	91 (*S*)	90	3
	(+)-(**1**)	91 (*R*)	90	3
p-Tol–S–*i*-Pr	(−)-(**1**)	66 (*S*)	95	6
p-Tol–S–Bn	(−)-(**1**)	94 (*S*)	95	3
Ph–S–cyclopropyl	(−)-(**1**)	92 (*S*)	90	18
t-Bu–S–Me	(−)-(**1**)	94 (*S*)	90	18
	(+)-(**1**)	94 (*S*)	90	18
t-Bu–S–Bn	(+)-(**1**)	91 (*S*)	80	48
	(+)-(**1**) (65 °C)	85 (*S*)	80	1
Bn–S–Me	(−)-(**1**)	13 (*S*)	94	3
Ph–S–CH=CH$_2$	(−)-(**1**)	85 (*S*)	60	48
Ph–S–CH$_2$CO$_2$Me	(−)-(**1**)	94 (*S*)	65	48
Ph–S–CH$_2$CN	(−)-(**1**)	>95 (*S*)	45	48
	(−)-(**1**)	86 (*S*)	84	96[8c]
	(−)-(**1**)	42 (*S*)	87	18[10]
	(−)-(**1**)	64 (*S*)	87	6[10]

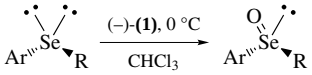
[a] At rt in CCl_4.



(3)

R = Ph 13:1 65%
R = Me 1.5:1 85%

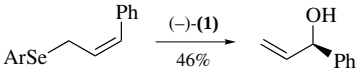
Asymmetric Oxidation of Selenides to Selenoxides. The difficulty in preparing optically active selenoxides is that they are configurationally unstable, forming achiral hydrates, $ArSe(OH)_2R$, with trace amounts of water.[12] Enantioselective oxidation of alkyl aryl selenides by (−)-(**1**), because of its aprotic nature, gives the selenoxides in 91% to >95% ee (eq 4). Oxidations are carried out as before (eq 2) except that moisture and trace amounts of acids in the solvents need to be rigorously excluded. The optically active selenoxides (Ar = 2,4,6-triisopropylphenyl) can be isolated by chromatography on basic alumina, but with some racemization (85–87% ee).[12]



(4)

Ar = Ph, 2,4,6-*i*-Pr$_3$C$_6$H$_2$; R = Me, Et, CH$_2$C$_6$H$_4$OMe-*p*

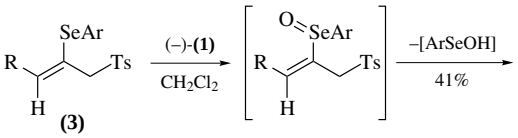
Asymmetric oxidation of allylic selenides gives allylic alcohols via a [2,3]-sigmatropic selenoxide–selenate rearrangement (eq 5).[2] In both oxidations, eqs 4 and 5, the configuration at the selenoxide is that predicted based on the sulfoxide model.



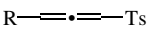
(5)

Ar = 2,4,6-*i*-Pr$_3$C$_6$H$_2$

Aryl vinyl selenides (**3**) are oxidized by (−)-(**1**) to selenoxide intermediates which undergo elimination to chiral allenic sulfones (eq 6).[12] Somewhat better ee values were observed using the modified Sharpless reagent (up to 38% ee). Asymmetric oxidation of cyclohexyl selenides by oxaziridine (−)-(**1**) give axially chiral cyclohexylidene derivatives in up to 83% ee (eq 7).[13]

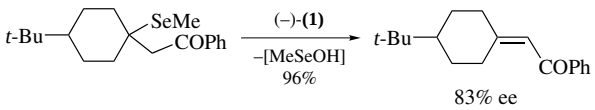


R = Pr, Ar = *o*-O$_2$NC$_6$H$_4$



(6)

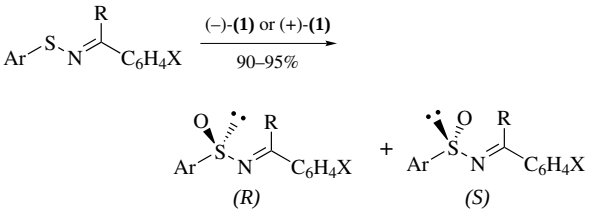
(*R*) 28% ee



(7)

83% ee

Asymmetric Oxidation of Sulfenimines to Sulfinimines. Enantiopure sulfinimines are ammonia imine synthons useful in the asymmetric synthesis of amines and β-amino acid derivatives.[3,14,15] Sulfinimines unavailable via the Andersen synthesis (R = H)[14,15] are prepared by asymmetric oxidation of the sulfenimines, ArS–N=C(R)PhX, with (+)-(**1**) or (−)-(**1**) at −20 to 20 °C in CCl_4 (eq 8).[3] Crystallization improves the ee to >95%. The sulfoxide chiral recognition model correctly predicts the configuration of the product.



(8)

Ar = Ph, R = X = H (–)-(**1**) 88% ee (*R*)
Ar = Ph, R = X = H (+)-(**1**) 88% ee (*S*)
Ar = *p*-Tolyl, R = Me, X = H (–)-(**1**) 87% ee (*R*)

1. Davis, F. A.; Thimma Reddy, R.; Han, W.; Carroll, P. J., *J. Am. Chem. Soc.* **1992**, *114*, 1428.
2. Davis, F. A.; Thimma Reddy, R., *J. Org. Chem.* **1992**, *57*, 2599.
3. Davis, F. A.; Thimma Reddy, R.; Reddy, R. E., *J. Org. Chem.* **1992**, *57*, 6387.
4. Davis, F. A.; Thimma Reddy, R.; Han, W.; Reddy, R. E., *Pure Appl. Chem.* **1993**, *65*, 633.
5. Mergelsberg, I.; Gala, D.; Scherer, D.; DiBenedetto, D.; Tanner, M., *Tetrahedron Lett.* **1992**, *33*, 161.
6. For reviews on the synthesis and application of chiral sulfoxides, see:(a) Posner, G. H. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport Z.; Stirling, C. J. M., Eds.; Wiley: Chichester, 1988; Chapter 16, p 823. (b) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; 2, Chapter 8, p 225. (c) Barbachyn, M. R.; Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D.; Scott, J. W., Eds.; Academic: New York, 1983; 4, Chapter 2; p 227. (d) Solladié, G., *Synthesis* **1981**, 185.
7. Andersen, K. K. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C. J. M., Eds.; Wiley: Chichester, 1988; Chapter 3, p 55.
8. (a) Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B., *J. Org. Chem.* **1991**, *56*, 5991. (b) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D., *J. Am. Chem. Soc.* **1992**, *114*, 5977. (c) Marino, J. P.; Bogdan, S.; Kimura, K., *J. Am. Chem. Soc.* **1992**, *114*, 5566.
9. Zhao, S. H.; Samuel, O.; Kagan, H. B., *Tetrahedron* **1987**, *43*, 5135 and references cited therein.
10. Rossi, C.; Fauve, A.; Madesclaire, M.; Roche, D.; Davis, F. A.; Thimma Reddy, R., *Tetrahedron: Asymmetry* **1992**, *3*, 629.
11. Rayner, C. M.; Sin, M. S.; Westwell, A. D., *Tetrahedron Lett.* **1992**, *33*, 7237.
12. Komatsu, N.; Murakami, T.; Nishibayashi, Y.; Sugita, T.; Uemura, S., *J. Org. Chem.* **1993**, *58*, 3697.
13. Komatsu, N.; Matsunaga, S.; Sugita, T.; Uemura, S., *J. Am. Chem. Soc.* **1993**, *115*, 5847.
14. Annunziata, R.; Cinquini, M.; Cozzi, F., *J. Chem. Soc., Perkin Trans. 1* **1982**, 339.
15. Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S., *J. Org. Chem.* **1991**, *56*, 4.

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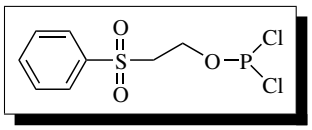
(2-Phenylsulfonyl)ethoxy Dichlorophosphine



[98288-60-9] $C_8H_9Cl_2O_3PS$ (MW 287.10)

InChI = 1/C8H9Cl2O3PS/c9-14(10)13-6-7-15(11,12)8-4-2-1-3-5-8/h1-5H,6-7H2

InChIKey = XJOUCQQGJUEPDI-UHFFFAOYAY

(reagent used for the synthesis of nucleotides by phosphoramidite method)

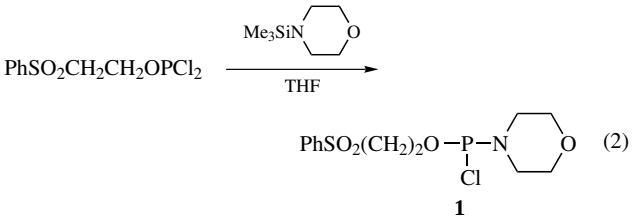
Physical Data: mp 32–35 °C;[1] ^{1}H NMR;[1] ^{31}P NMR;[1] stable for at least one year when stored at −18 °C.[1]

Preparative Methods: **1** can be prepared from phenylsulfonylethanol with an excess of phosphorus trichloride in acetonitrile solution without the use of a base (eq 1).

$$PhSO_2CH_2CH_2OH \xrightarrow[\text{rt, 10 min}]{PCl_3\ (7\ \text{equiv}),\ CH_3CN} PhSO_2CH_2CH_2OPCl_2 \quad (1)$$

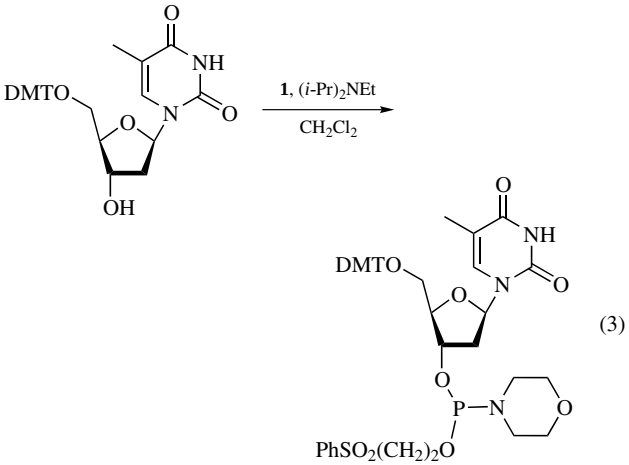
97%

Nucleotide Synthesis by the Phosphoramidite Method. (2-Phenylsulfonyl)ethoxy dichlorophosphine is readily converted into the corresponding crystalline phosphoromorpholido chloridite (**1**) on exposure to *N*-trimethylsilylmorpholine (eq 2). This substance then reacts with 5′-*O*-protected nucleosides to give the 3′-*O*-phosphoromorpholodites which are typically solids and may be purified by column chromatography. For example, the reaction with 5′-*O*-(dimethoxytrityl)thymidine gave corresponding phosphoromorpholodite (eq 3). **1** has been used to synthesize the thymidine decamer on a solid support using 1-hydroxybenzotriazole as the promoter and the usual combination of iodine and water to effect oxidation to the phosphate after coupling.[2]



(2)

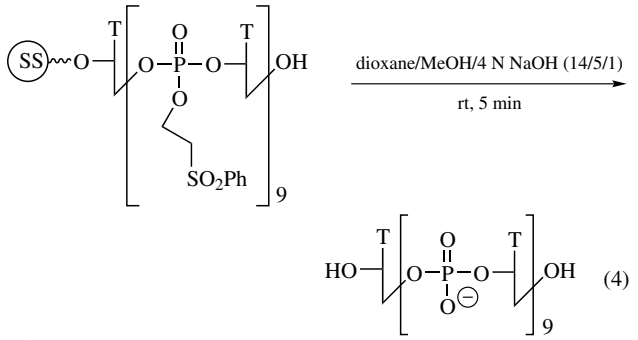
1



(3)

(2-Phenylsulfonyl)ethyl phosphites and phosphates are stable in the presence of acids, towards acid, hydrogenolysis, and tertiary amines in aprotic solvents, enabling the orthogonal removal of numerous other protecting groups.

Following coupling and oxidation to the phosphate oxidation level, deprotection is achieved rapidly and cleanly by β-elimination in the presence of the mixture of dioxane/methanol/4 N NaOH(14/5/1) in 5 min (eq 4).[1,3]



SS = solid support, T = thymine

1. Claesen, C. A. A.; Segers, R. P. A. M.; Tesser, G. I., *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 119.
2. Claesen, C. A. A.; Segers, R. P. A. M.; Tesser, G. I., *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 209.
3. (a) Claesen, C.; Tesser, G. I.; Dreef, C. E.; Marugg, J. E.; van der Marel, G. A.; van Boom, J. H., *Tetrahedron Lett.* **1984**, *25*, 1307. (b) Beld, A.; Claesen, C. A. A.; Roersma, E. S.; Schippers, W. J. M.; Keizer, L. M.; Tesser, G. I., *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 196.

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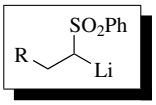
α-Phenylsulfonylethyllithium



(R = H)

[69291-71-0] $C_8H_9LiO_2S$ (MW 176.18)

InChI = 1/C8H9O2S.Li/c1-2-11(9,10)8-6-4-3-5-7-8;/h2-7H, 1H3;/ rC8H9LiO2S/c1-7(9)12(10,11)8-5-3-2-4-6-8/ h2-7H,1H3

InChIKey = CVMBHCCOALYSGQ-ATIKTPKWAQ

(versatile stabilized carbon nucleophile for forming C–C, C=C, and C≡C bonds with a wide range of carbon and heteroatom electrophiles[1–3])

Physical Data: pK_a in DMSO 31.0.

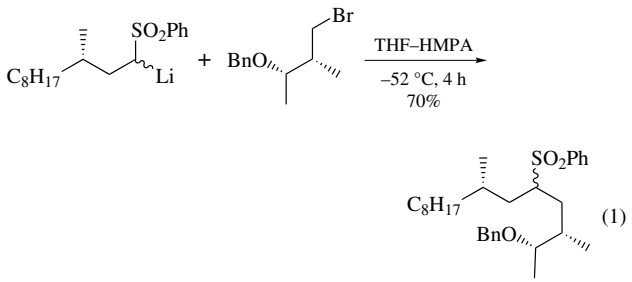
Solubility: sol THF, Et_2O.

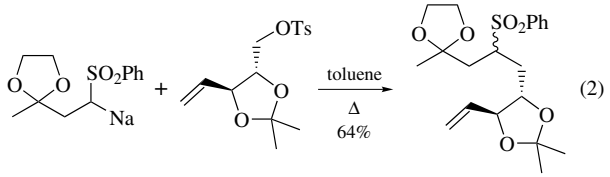
Preparative Methods: prepared in situ as needed by metalation of ethyl phenyl sulfone with butyllithium or lithium diisopropylamide.

Handling, Storage, and Precautions: moisture sensitive; handle under nitrogen or argon.

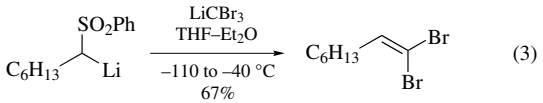
General Considerations. The sulfone group is perhaps second only to the carbonyl group in its versatility and utility. It serves the dual role of C–H activator and leaving group under a wide range of conditions,[1] thereby enabling creation of up to three C–C bonds from a single functional group. Alkyl aryl sulfones have a pK_a of ca. 31 and are therefore quantitatively deprotonated by strong bases such as butyllithium, lithium diisopropylamide, or Grignard reagents. The resultant colored carbanions (yellow or red–orange)[4] are usually stable at rt. It is also possible to form an α,α-dianion which reacts with even relatively poor electrophiles.[5] In the following discussion, α-phenylsulfonylethyllithium serves as a paradigm for the class of 'a^1d^1' reagents represented by $ArSO_2$–CH(M)R.

α-Phenylsulfonylethyllithiums as Donors. α-Arylsulfonylalkyllithiums react with all the typical carbon electrophiles to form a C–C bond in generally good yield; some indication of the scope of the procedure can be gleaned from eqs 1–9. For example, alkylation with primary alkyl bromides (or iodides; eq 1),[6] tosylates (eq 2),[7] or triflates[8] occurs even when there is an α-branch in the chain. In the case of sluggish reactions, additives such as hexamethylphosphoric triamide or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine can be added to accelerate alkylation.

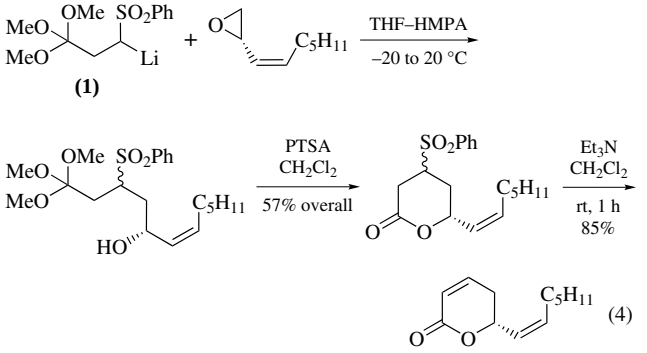




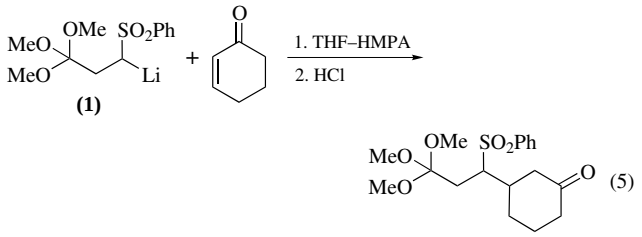
The reaction of sulfonyl carbanions with halocarbenoids gives a 1,1-dibromoalkene or a 1-bromoalkene (eq 3).[9] The reaction probably does not involve a carbene intermediate.



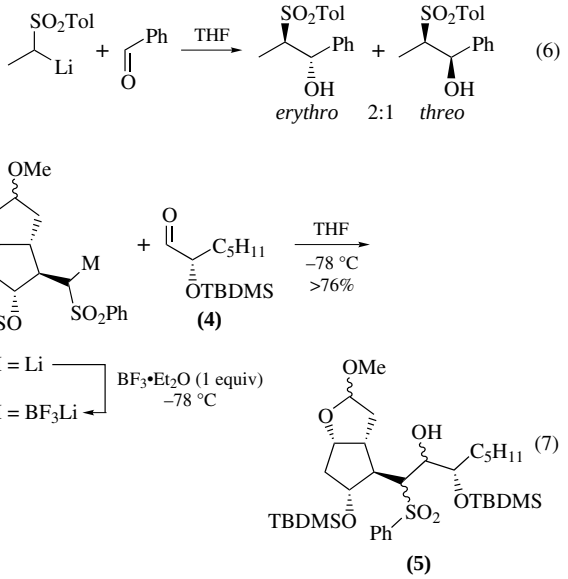
Terminal epoxides react slowly with sulfonyl carbanions such as the homoenolate equivalent (**1**) (eq 4).[10] With disubstituted epoxides and cyclic epoxides the reactions are slower still. For example, reaction of the lithio derivative of ethyl phenyl sulfone with cyclopentene oxide occurs in excellent yield (98%) after 10 h reflux in toluene.[11] It has been reported that, in some cases, the addition of a Lewis acid (magnesium bromide,[12] boron trifluoride etherate,[13,14] titanium tetraisopropoxide,[15] MeOAl(*i*-Bu)$_2$[16]) or HMPA[17] improves the yield dramatically.



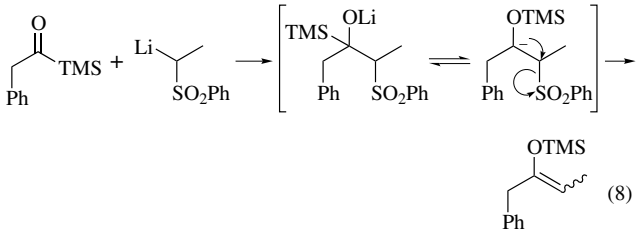
In the presence of HMPA, the homoenolate equivalent (**1**) underwent conjugate addition to cyclohexenone. In the absence of HMPA, a mixture of 1,2- and 1,4-adducts was obtained (eq 5).[18,19]



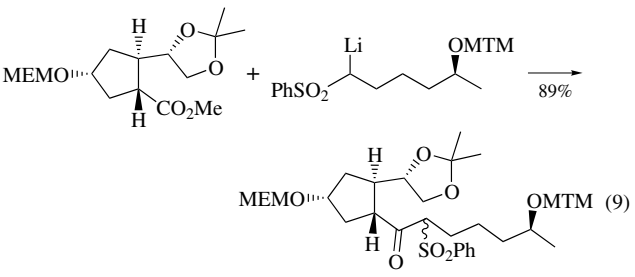
The addition of metalated sulfones to aldehydes is reversible and in simple cases the reaction displays modest selectivity for the *erythro* isomer (eq 6).[20] The reverse reaction is favored when the adducts are sterically compressed (e.g. ketone adducts) or when the sulfone anion is stabilized by conjugation (i.e. allylic or benzylic sulfones) or proximate heteroatoms. However, in unfavorable cases the position of the equilibrium can be tuned by varying the metal. For example, the lithio sulfone (**2**) did not give a stable adduct with aldehyde (**4**) but the 'ate' complex derived from the lithio derivative and BF_3 gave the desired adduct (**5**) (eq 7).[21]



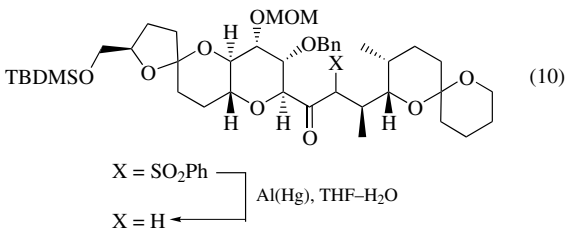
α-Phenylsulfonylethyllithium adds to acylsilanes to give an adduct which undergoes a Brook rearrangement with subsequent loss of benzenesulfinate anion. The product of the reaction is an enol silane (eq 8).[22]



Reaction of the metalated sulfones with esters,[23,24] lactones,[25,26] amides and carbonates[27] leads to the corresponding β-keto sulfone (eq 9).[23] The β-keto sulfones thus formed display chemistry reminiscent of β-keto esters in their enhanced acidity and tendency to undergo *C*- and *O*-alkylation and acylation.

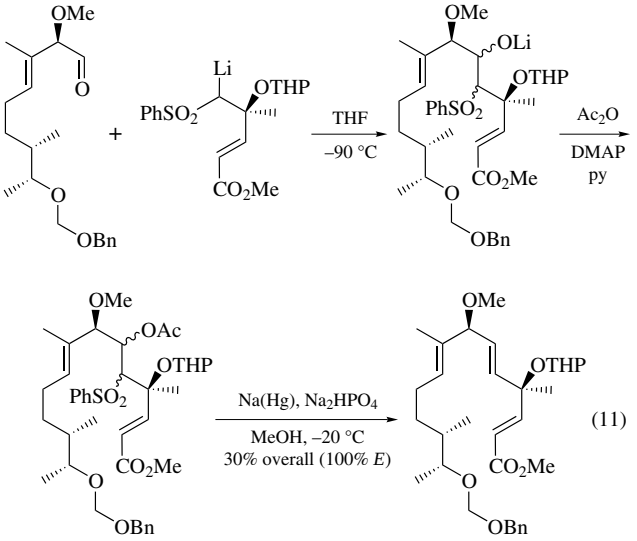


Aryl Sulfones as Acceptors: Desulfonylation Reactions. The sulfone group is a powerful electron acceptor which can be cleaved under a wide range of conditions. We have already seen that mild base will cause elimination of benzenesulfinate from β-arylsulfonyl-substituted carbonyl derivatives (eq 5). α-Arylsulfonyl-substituted carbonyl derivatives undergo reductive desulfonylation[28] under very mild conditions using aluminum amalgam (eq 10),[29] but in the absence of carbonyl activation, reductive cleavage of the sulfone group requires much stronger reducing agents such as sodium amalgam in MeOH buffered with Na_2HPO_4,[30] sodium–ammonia,[31] magnesium in refluxing MeOH,[32] or samarium(II) iodide in THF–HMPA.[33]

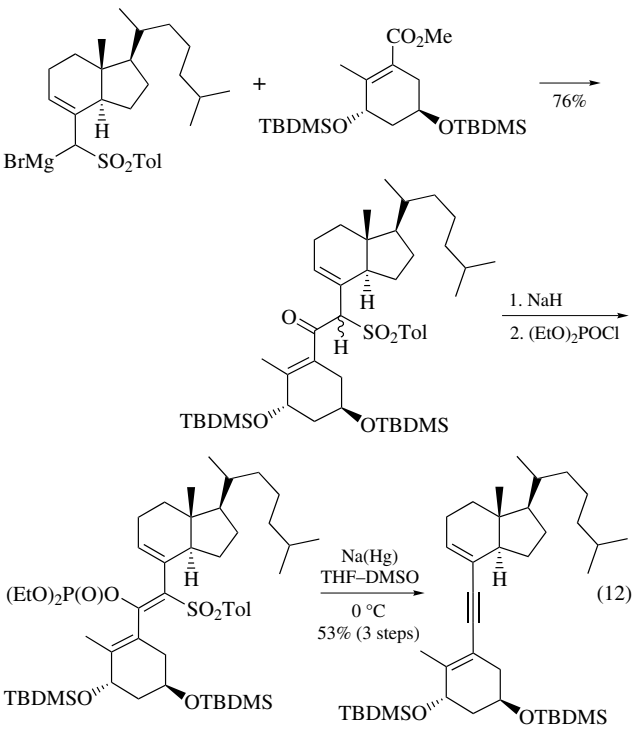


The Julia Alkenation and Related Reactions. In 1973, Julia and Paris[34] reported a new connective and regioselective alkene synthesis (eq 10) based on the reductive elimination of β-acyloxy sulfones. The Julia alkenation is now one of the principal methods for fragment linkage in complex natural product synthesis.[35,36] Mono-, di-, tri-, and tetrasubstituted alkenes can be prepared in moderate to good yield, depending on the substrate. The three-step sequence, illustrated in eq 11, entails (a) condensation of a metalated sulfone with an aldehyde or ketone, (b) *O*-functionalization of the adduct as the acetate, benzoate, or mesylate (to prevent retroaldolization), and (c) reductive elimination using 6% Na(Hg) in THF–MeOH (3:1) at −20 °C.[37] In favorable cases, step (b) can be omitted and the reductive elimination performed on a

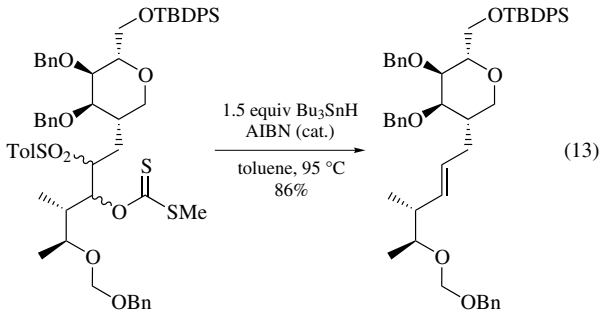
β-hydroxy sulfone intermediate. Potential problems attending each step have been summarized.[35]



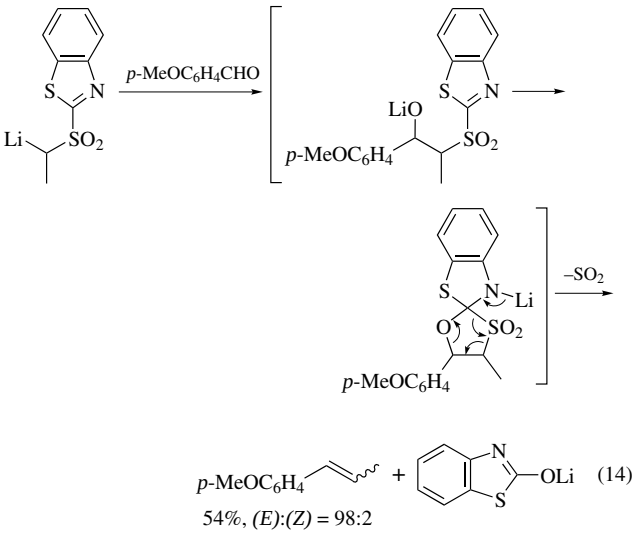
A detailed investigation of the scope and stereochemistry of the reductive elimination leading to 1,2-disubstituted alkenes revealed high *trans* stereoselectivity which is *independent* of the stereochemistry of the β-acyloxy sulfone adducts.[37,38] Furthermore, the stereoselectivity increases with increasing steric congestion about the nascent alkene and maximum yields and rate are observed for the formation of conjugated dienes and trienes. The Julia procedure has also been adapted to the synthesis of alkynes (eq 12).[39,40]



There are two further variants of the Julia alkenation which deserve wider recognition. Both methods surmount the inherent limitation in scale of the reductive elimination step imposed by the use of Na(Hg). The first method involves a radical-induced elimination of thiocarbonyl derivatives of β-hydroxy sulfones,[41] as illustrated in eq 13.[42]

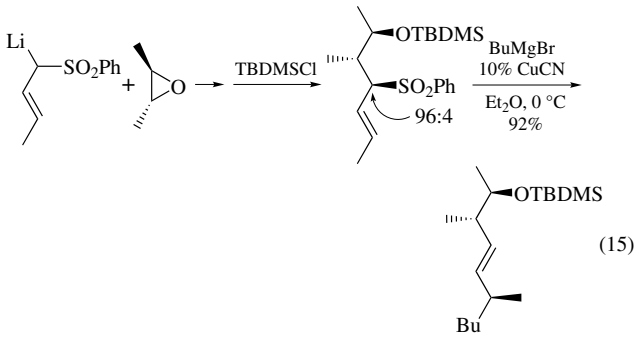


The second recent variant, developed by Julia and co-workers, avoids reductive elimination altogether and provides a remarkable one-pot connective synthesis of alkenes.[43] The procedure, illustrated in eq 14, involves condensation of an aldehyde or ketone with a lithiated benzothiazolyl alkyl sulfone to give an adduct which first cyclizes and then fragments with extrusion of sulfur dioxide, benzothiazolone (which then tautomerizes to 2-hydroxybenzothiazole), and the alkene. Generally a mixture of (*E*)- and (*Z*)-alkenes is obtained, but in sterically hindered substrates the (*E*) isomer can be obtained selectively. The same reaction has been observed with the pyridinyl sulfone analogs, in which case the separable β-hydroxy sulfone intermediates undergo stereospecific *anti* elimination to the corresponding alkene.



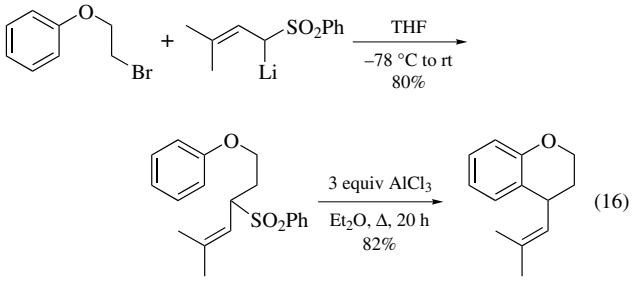
Alternative Desulfonylation/C–C Bond-forming Procedures. The foregoing discussion has focussed on reductive methods for removing sulfones and, in the case of the Julia alkenation, desulfonylation is accompanied by the formation of a new C–C bond. Another method which accomplishes desulfonylation with the concomitant construction of a C=C bond entails fluoride-induced elimination of β-silyl sulfones.

Allylic sulfones undergo S_N2' displacement by cyanocuprates with high *syn* stereoselectivity (eq 15).[44] Stabilized enolates also displace allylic arylsulfonyl groups in the presence of Pd^0 or Ni^0 catalysts.[45]



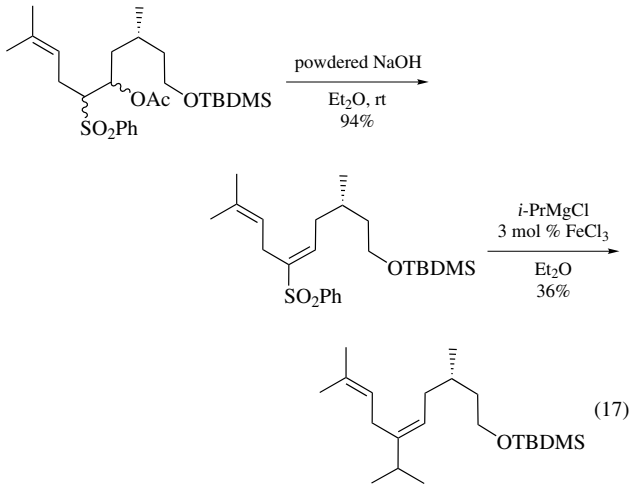
(15)

Allylic and tertiary alkyl sulfones can also participate in electrophilic cyclizations in the presence of aluminum chloride (Friedel–Crafts reaction; eq 16).[46]



(16)

Base-catalyzed elimination of β-acetoxy sulfones is highly stereoselective, leading to (*E*)-alkenyl sulfones which undergo transition metal-catalyzed coupling with Grignard reagents with retention of configuration to provide a stereoselective synthesis of trisubstituted alkenes.[47] Either nickel(II) acetylacetonate, tris(acetylacetonato)iron(III), or iron(III) chloride can be used as the catalyst (eq 17).[48]



(17)

Oxidative Desulfonylation of Arylsulfonylalkyllithiums. Aryloxysulfonylalkyllithiums can be converted to ketones in one pot by reaction with oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide),[49] bis(trimethylsilyl) peroxide,[50] or chlorodimethoxyborane/*m*-chloroperbenzoic acid.[51]

Related Reagents. Methyl Phenyl Sulfone; 4-Phenylsulfonyl-2-butanone Ethylene Acetal; 3-(Phenylsulfonyl)propanal Ethylene Acetal.

1. *The Chemistry of Sulphoxides and Sulphones*; Patai, S.; Rappoport, Z.; Stirling, C.; Eds.; Wiley: New York, 1988.
2. Solladié, G., *Comprehensive Organic Synthesis* **1991**, *6*, 133.
3. Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: Oxford, 1993.
4. Bongini, A.; Savoia, D.; Umani-Ronchi, A., *J. Organomet. Chem.* **1976**, *112*, 1.
5. Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R., *J. Org. Chem.* **1988**, *53*, 1922.
6. Larchevêque, M.; Sanner, C.; Azerad, R.; Buisson, D., *Tetrahedron* **1988**, *44*, 6407.
7. Wershofen, S.; Scharf, H.-D., *Synthesis* **1988**, 854.
8. Kennedy, R. M.; Abiko, A.; Takemasa, T.; Okumoto, H.; Masamune, S., *Tetrahedron Lett.* **1988**, *29*, 451.
9. Charreau, P.; Julia, M.; Verpeaux, J.-N., *Bull. Soc. Chem. Fr. Part 2* **1990**, *127*, 275.
10. Carretero, J. C.; Ghosez, L., *Tetrahedron Lett.* **1988**, *29*, 2059.
11. Nwaukwa, S. O.; Lee, S.; Keehn, P. M., *Synth. Commun.* **1986**, *16*, 309.
12. Marshall, J. A.; Andrews, R. C., *J. Org. Chem.* **1985**, *50*, 1602.
13. Nakata, T.; Saito, K.; Oishi, T., *Tetrahedron Lett.* **1986**, *27*, 6345.
14. Achmatowicz, B.; Marzak, S.; Wicha, J., *J. Chem. Soc., Chem. Commun.* **1987**, 1226.
15. Greck, C.; Grice, P.; Ley, S. V.; Wonnacott, A., *Tetrahedron Lett.* **1986**, *27*, 5277.
16. Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B., *J. Org. Chem.* **1987**, *52*, 3759.
17. Scherkenbeck, J.; Barth, M.; Thiel, U.; Metten, K.-H.; Heinemann, F.; Welzel, P., *Tetrahedron* **1988**, *44*, 6325.
18. De Lombaert, S.; Nemery, I.; Roekens, B.; Carretero, J. C.; Kimmel, T.; Ghosez, L., *Tetrahedron Lett.* **1986**, *27*, 5099.
19. Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C., *J. Org. Chem.* **1989**, *54*, 1960.
20. Truce, W. E.; Klingler, T. C., *J. Org. Chem.* **1970**, *35*, 1834.
21. Achmatowicz, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J.; Wicha, J., *Tetrahedron Lett.* **1985**, *26*, 5597.
22. Reich, H. J.; Rusek, J. J.; Olson, R. E., *J. Am. Chem. Soc.* **1979**, *101*, 2225.
23. Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H., *J. Am. Chem. Soc.* **1986**, *108*, 284.
24. Julia, M.; Launay, M.; Stacino, J.-P.; Verpeaux, J.-N., *Tetrahedron Lett.* **1982**, *23*, 2465.
25. Brimble, M. A.; Rush, C. J.; Williams, G. M.; Baker, E. N., *J. Chem. Soc., Perkin Trans. 1* **1990**, 414.
26. Brimble, M. A.; Officer, D. L.; Williams, G. M., *Tetrahedron Lett.* **1988**, *29*, 3609.
27. Babudri, F.; Florio, S.; Vitrani, A. M.; Di Nunno, L., *J. Chem. Soc., Perkin Trans. 1* **1984**, 1899.
28. Corey, E. J.; Chaykovsky, M., *J. Am. Chem. Soc.* **1965**, *87*, 1345.
29. Isobe, M.; Ichikawa, Y.; Bai, D.-L.; Masaki, H.; Goto, T., *Tetrahedron* **1987**, *43*, 4767.
30. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R., *Tetrahedron Lett.* **1976**, 3477.
31. Marshall, J. A.; Cleary, D. G., *J. Org. Chem.* **1986**, *51*, 858.
32. Brown, A. C.; Carpino, L. A., *J. Org. Chem.* **1985**, *50*, 1749.
33. Künzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R., *Tetrahedron Lett.* **1991**, *32*, 1949.

34. Julia, M.; Paris, J.-M., *Tetrahedron Lett.* **1973**, 4833.
35. Kocienski, P. J., *Comprehensive Organic Synthesis* **1991**, *6*, 975.
36. Kelly, S. E., *Comprehensive Organic Synthesis* **1991**, *1*, 729.
37. Kocienski, P. J.; Lythgoe, B.; Ruston, S., *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.
38. Kocienski, P. J.; Lythgoe, B.; Roberts, D. A., *J. Chem. Soc., Perkin Trans. 1* **1978**, 834.
39. Lythgoe, B.; Waterhouse, I., *J. Chem. Soc., Perkin Trans. 1* **1980**, 1405.
40. Bartlett, P.; Green, F. R.; Rose, E. H., *J. Am. Chem. Soc.* **1978**, *100*, 4852.
41. Lythgoe, B.; Waterhouse, I., *Tetrahedron Lett.* **1977**, 4223.
42. Williams, D. R.; Moore, J. L.; Yamada, M., *J. Org. Chem.* **1986**, *51*, 3916.
43. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O., *Bull. Soc. Chem. Fr. Part 2* **1993**, *130*, 336.
44. Trost, B. M.; Merlic, C. A., *J. Am. Chem. Soc.* **1988**, *110*, 5216.
45. Trost, B. M.; Schmuff, N. R.; Miller, M. J., *J. Am. Chem. Soc.* **1980**, *102*, 5979.
46. Trost, B. M.; Ghadiri, M. R., *J. Am. Chem. Soc.* **1984**, *106*, 7260.
47. Fabre, J.-L.; Julia, M.; Verpeaux, J.-N., *Bull. Soc. Chem. Fr.* **1985**, 772.
48. Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M., *Tetrahedron* **1988**, *44*, 111.
49. Little, R. D.; Myong, S. O., *Tetrahedron Lett.* **1980**, *21*, 3339.
50. Hwu, J. R., *J. Org. Chem.* **1983**, *48*, 4432.
51. Baudin, J.-B.; Julia, M.; Rolando, C., *Tetrahedron Lett.* **1985**, *26*, 2333.

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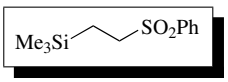
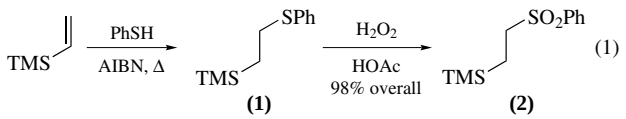
(2-Phenylsulfonylethyl)trimethylsilane



[73476-18-3] $C_{11}H_{18}O_2SSi$ (MW 242.45)
InChI = 1/C11H18O2SSi/c1-15(2,3)10-9-14(12,13)11-7-5-4-6-8-11/h4-8H,9-10H2,1-3H3
InChIKey = IVPQHMQOYMNETK-UHFFFAOYAW

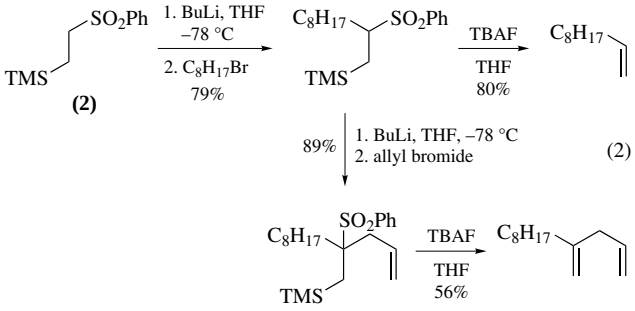
(reagent for the synthesis of mono- and 1,1-disubstituted alkenes via sulfone metalation, alkylation, and fluoride-induced elimination[1])

Physical Data: mp 52 °C.
Solubility: sol all common ethereal, halocarbon, and hydrocarbon solvents.
Form Supplied in: solid; commercially available.
Preparative Methods: (2-phenylsulfonylethyl)trimethylsilane (**2**) is prepared by radical addition of thiophenol to vinyltrimethylsilane to give (2-phenylthioethyl)trimethylsilane (**1**), which is then oxidized with hydrogen peroxide (eq 1).[2,3]



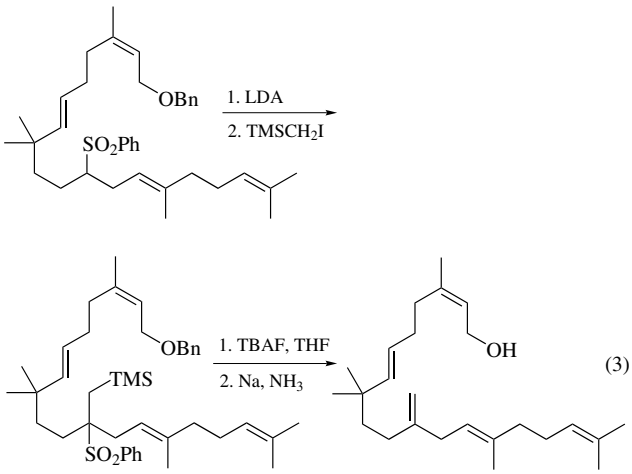
(1)

General Considerations. A sequence involving metalation, alkylation, and fluoride-induced elimination of benzenesulfinate allows the conversion of (**2**) to a terminal alkene. An analogous sequence involving a double alkylation of (**2**) provides a 1,1-disubstituted alkene (eq 2).[4,5] The lithio derivative of (**2**) has also been used to prepare cyclopropylidene derivatives,[6] homoallylic alcohols,[7] and allyl silanes via the Julia alkenation.[3]



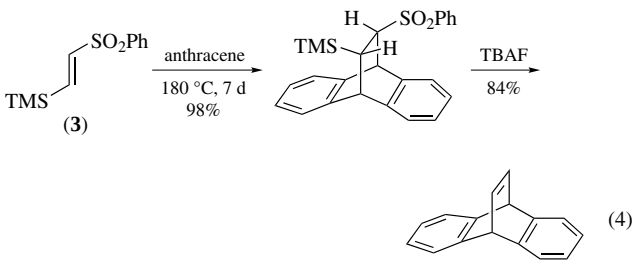
(2)

Alternative Routes to Substituted (2-Phenylsulfonylethyl)-trimethylsilanes. Although the fluoride-induced elimination is a reliable and efficient method for synthesizing alkenes, the requisite silyl sulfone precursors are often better prepared by methods which avoid the use of (**2**). For example, eq 3 illustrates an alternative synthesis of 2,2-dialkyl-2-(phenylsulfonylethyl)trimethylsilanes involving alkylation of a lithio sulfone with (iodomethyl)-trimethylsilane.[8,9]



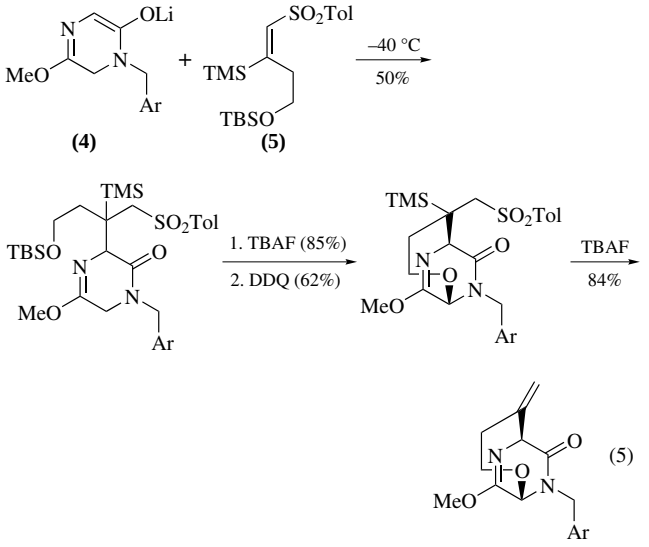
(3)

2-(Phenylsulfonylvinyl)trimethylsilane (**3**) is a useful acetylene equivalent for use in Diels–Alder reactions (eq 4).[10,11]



(4)

Phenylsulfonylethylene derivatives undergo conjugate addition reactions. Thus (**3**) reacts with unsaturated Grignard reagents and organocuprates,[12] while the substituted sulfone (**5**) undergoes conjugate addition by the enolate derivative (**4**) to give a bicyclomycin intermediate (eq 5).[13]



Related Reagents. 1,1-Bis(phenylsulfonyl)ethylene; Phenylsulfonylethylene; α-Phenylsulfonylethyllithium; 1-Phenylsulfonyl-2-(trimethylsilyl)acetylene; (*E*)-1-Phenylsulfonyl-2-trimethylsilylethylene; Phenylsulfonyl(trimethylsilyl)methane.

1. Kocienski, P. J., *Comprehensive Organic Synthesis* **1991**, *6*, 1002.
2. Hsiao, C.-N.; Shechter, H., *Tetrahedron Lett.* **1982**, *23*, 1963.
3. Hsiao, C.-N.; Shechter, H., *J. Org. Chem.* **1988**, *53*, 2688.
4. Kocienski, P. J., *Tetrahedron Lett.* **1979**, *20*, 2649.
5. Nájera, C.; Sansano, J. M., *Tetrahedron Lett.* **1993**, *34*, 3781.
6. Hsiao, C.-N.; Hannick, S. M., *Tetrahedron Lett.* **1990**, *31*, 6609.
7. Kabat, M. M.; Wicha, J., *Tetrahedron Lett.* **1991**, *32*, 1073.
8. Kocienski, P. J., *J. Org. Chem.* **1980**, *45*, 2037.
9. Kocienski, P. J.; Todd, M., *J. Chem. Soc., Perkin Trans. 1* **1983**, 1777, 1783.
10. Paquette, L. A.; Williams, R. V., *Tetrahedron Lett.* **1981**, *22*, 4643.
11. Carr, R. V. C.; Williams, R. V.; Paquette, L. A., *J. Org. Chem.* **1983**, *48*, 4976.
12. Eisch, J. J.; Behrooz, M.; Dua, S. K., *J. Organomet. Chem.* **1985**, *285*, 121.
13. Dawson, I. M.; Gregory, J. A.; Herbert, R. B.; Sammes, P. G., *J. Chem. Soc., Chem. Commun.* **1986**, 620.

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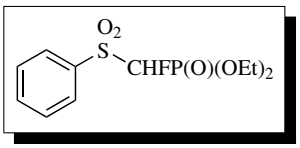
Phenylsulfonylfluoromethylphosphonate



[114968-97-7] $C_{11}H_{16}FPO_5S$ (MW 311.05)

InChI = 1/C11H16FO5PS/c1-3-16-18(13,17-4-2)11(12)19(14,15)10-8-6-5-7-9-10/h5-9,11H,3-4H2,1-2H3

InChIKey = HUOWVYVTKZRXGM-UHFFFAOYAA

(reagent used in stereospecific synthesis of α-fluoro-α,β-unsaturated sulfones and terminal vinyl fluorides)

Physical Data: mp 62–64 °C.

Solubility: soluble in THF, DMF, and HMPA.

Form Supplied in: white solid.

Preparative Methods: the title reagent could be prepared through the reaction of the potassium salt of phenylsulfonylmethylphosphonate with an electrophilic fluorinating reagent such as $FClO_3$ (eq 1)[1] or SELECTFLUOR™ (eq 2).[2] This compound could also be synthesized through the coupling of fluoromethyl phenyl sulfone and diethyl chlorophosphate in the presence of LiHMDS in THF cooled to less than −70 °C (eq 3).[3,4]

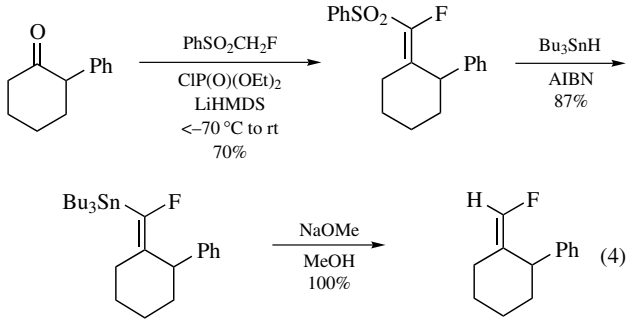
$$PhSO_2CH_2P(O)(OEt)_2 \xrightarrow[0\text{–}15\ ^\circ C,\ 0.5\text{–}1\ h\ \ 50\text{–}60\%]{FClO_3,\ KH,\ THF} PhSO_2CHFP(O)(OEt)_2 \quad (1)$$

$$PhSO_2CH_2P(O)(OEt)_2 \xrightarrow[10\ min,\ rt\ \ SELECTFLUOR\ ^{TM}\ \ 61\%]{KH,\ t\text{-}BuOH,\ DMF} PhSO_2CHFP(O)(OEt)_2 \quad (2)$$

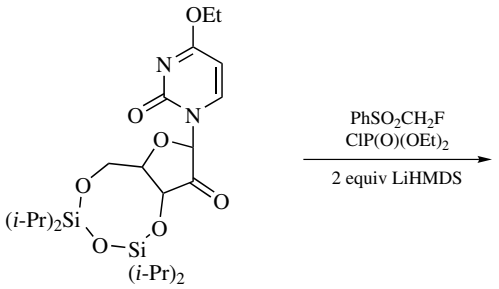
$$PhSO_2CH_2F \xrightarrow[LiHMDS\ \ THF,\ <\!-70\ ^\circ C\ \ 73\%]{ClP(O)(OEt)_2} PhSO_2CHFP(O)(OEt)_2 \quad (3)$$

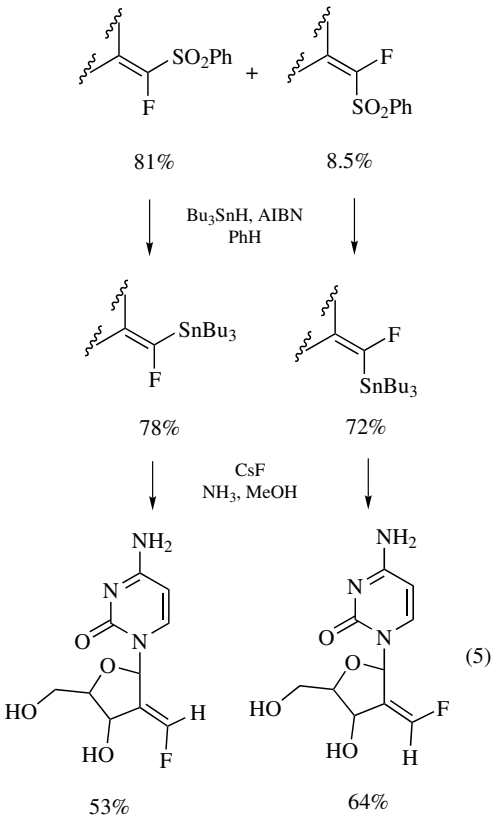
Purity: crystallization from a 2:1 mixture of toluene and heptane at −20 °C.

Reaction with Carbonyl Compounds. The carbanion of phenylsulfonylfluoromethylphosphonate could be readily generated when the phosphonate is treated with a strong base (LDA, BuLi, LiHMDS, NaH, KH, etc.). Alternatively, the anion could also be generated in situ by coupling of fluoromethyl phenyl sulfone, diethyl chlorophosphate, and 2 equiv of LiHMDS at −78 °C.[3] The resultant carbanion reacts with a variety of aldehydes and ketones, affording the corresponding α-fluoro-α,β-unsaturated sulfones in good to excellent yields.[1,3,5–9] In some cases, excellent stereoselectivity could be achieved. For example, reaction of α-phenyl cyclohexanone with the carbanion gives a 100% (*E*) product in 70% yield. The α-fluoro-α,β-unsaturated sulfone could be easily converted into the corresponding terminal vinyl fluoride in two simple steps (eq 4).[3] The method has been applied in the synthesis of 2′-deoxy-2′-fluoroethylene cytidine as potential inhibitors of ribonucleoside diphosphate reductase (eq 5).[5,8]



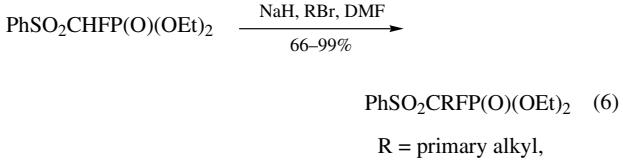
(4)



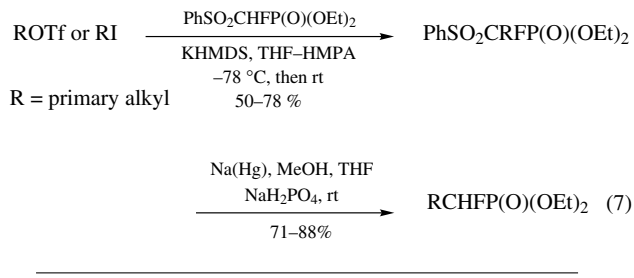


(5)

Reaction with Primary Alkyl Bromides, Iodides, or Triflates. Treatment of the sodium or potassium salt of phenylsulfonylfluoromethylphosphonate with primary alkyl bromides[1] (eq 6), iodides,[10] or triflates[10] (eq 7) affords (α-fluoro-α-phenylsulfonylalkyl)phosphonates in moderate to good yields, which could be converted to the corresponding (α-fluoroalkyl)phosphonates via Na(Hg)-mediated desulfonation (eq 7).[10]



(6)



(7)

1. Koizumi, T.; Hagi, T.; Horie, Y.; Takeuchi, Y., *Chem. Pharm. Bull.* **1987**, *35*, 3959.
2. Lal, G. S., *J. Org. Chem.* **1993**, *58*, 2791.
3. McCarthy, J. R.; Matthews, D. P.; Paolini, J. P., *Org. Synth.* **1993**, *72*, 216.
4. Appell, R. B., *Synth. Commun.* **1995**, *25*, 3583.
5. McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S., *J. Am. Chem. Soc.* **1991**, *113*, 7439.
6. McCarthy, J. R.; Matthews, D. P.; Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T., *Tetrahedron Lett.* **1990**, *31*, 5449.
7. Shen, Y. C.; Wang, G. P., *Org. Lett.* **2002**, *4*, 2083.
8. Matthews, D. P.; Persichetti, R. A.; Sabol, J. S.; Stewart, K. T.; McCarthy, J. R., *Nucleosides & Nucleotides* **1993**, *12*, 115.
9. Matthews, D. P.; Gross, R. S.; McCarthy, J. R., *Tetrahedron Lett.* **1994**, *35*, 1027.
10. Berkowitz, D. B.; Bose, M.; Asher, N. G., *Org. Lett.* **2001**, *3*, 2009.

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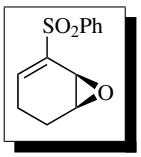
(1*S*,6*S*)-2-(Phenylsulfonyl)-7-oxabicyclo-[4.1.0]hept-2-ene



[195604-53-6] $C_{12}H_{12}O_3S$ (MW 236.29)

InChI = 1/C12H12O3S/c13-16(14,9-5-2-1-3-6-9)11-8-4-7-10-12(11)15-10/h1-3,5-6,8,10,12H,4,7H2/t10-,12-/m0/s1

InChIKey = CUIXDYPPWPJZND-JQWIXIFHBB

(reagent used as a versatile chiral scaffold in the expansion of six-membered rings or six-carbon acyclic fragments)

Physical Data: mp 96–97.5 °C; $[\alpha]_d$ = +88.7 (*c* = 0.52).

Solubility: soluble in THF, CH_2Cl_2, MeOH, benzene, toluene, DMF; slight soluble in Et_2O; insoluble in hexanes.

Form Supplied in: white crystalline solid.

Analysis of Reagent Purity: ^{1}H NMR, ^{13}C NMR; ee and purity determined by Chiral HPLC: Chiracel OJ, 4.6 × 250 mm^2 column eluting with 50:50 hexane:2-propanol, flow rate 1 mL/min, (*R*,*R*) retention time 20 min, (*S*,*S*) retention time 34 min.

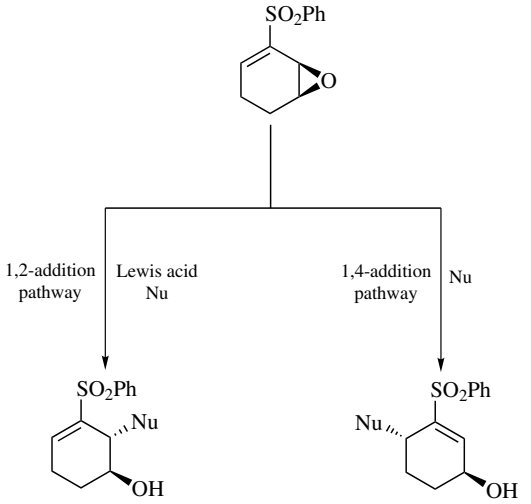
Preparative Methods: can be prepared from the epoxidation of 2-phenylsulfonyl-1,3-cyclohexadiene using

sodium hypochlorite-*N,N′*-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (Jacobsen's catalyst).[1a] Racemic material is readily available through epoxidation with *m*CPBA.[1b]

Handling, Storage, and Precautions: the white solid may be stored at room temperature for longer periods of time with no decomposition. No toxicity data is available.

Introduction. (1*S*,6*S*)-2-(Phenylsulfonyl)-7-oxabicyclo[4.1.0]hept-2-ene ($PhSO_2$CHD-epoxide) is a versatile chiral scaffold for the elaboration of six-membered rings or six-carbon acyclic fragments with one to four chiral centers. The flexibility to control the relative and absolute stereochemistry of every stereogenic center makes $PhSO_2$CHD-epoxide as valuable tool in the synthesis of natural products and unnatural analogs.

Addition of Nucleophiles 1,2 vs 1,4. The addition of various nucleophiles to $PhSO_2$CHD-epoxide can be controlled, with some exceptions, by careful choice of reaction conditions. The use of 'soft' nucleophiles takes advantage of the propensity of the vinyl sulfone to act as a Michael acceptor (eq 1). Neutral amines, enolates and their equivalents, cuprates, and sodium borohydride all provide the 1,4-*trans*-addition adduct in excellent yields. Alternatively, use of Lewis acids reverses this trend. For instance, amines with $LiClO_4$, $MgBr_2$, Me_2AlCl, and $TMSN_3$ with $Yb(OTf)_3$ furnish the 1,2-*trans*-addition product as the major isomer. Table 1 lists a variety of nucleophiles that add in a 1,2-fashion, and Table 2 lists a variety of nucleophiles that add in a 1,4-fashion.[2]



(1)

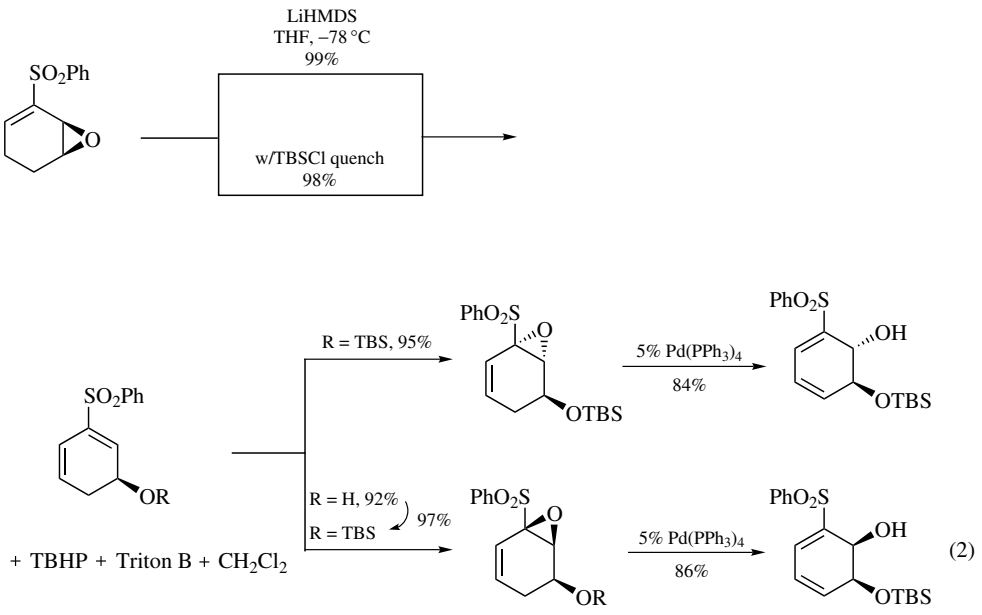
Table 1 1,2-Addition of nucleophiles

Nucleophile	Yield (%), 1,2-Addition
$MgBr_2$	91
Me_2AlCl	88 (Nu = Cl)
Pyrrolidine, $LiClO_4$	95 (>20:1)
DIBAL-H	46
$AlMe_3$, H_2O	76 (20:1)
$TMSN_3$, $Yb(OTf)_3$	92
TsOH, 4Å molecular sieves	84 (Nu = OTs)

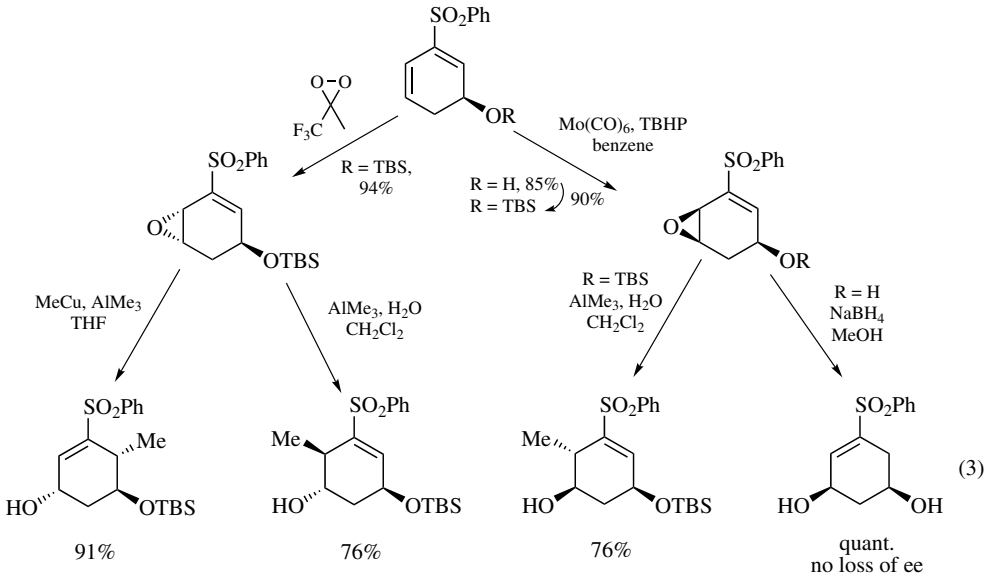
Table 2 1,4-Addition of nucleophiles

Nucleophile	Yield (%), 1,4-Addition
Pyrrolidine	99
$LiCH_2CO_2Me$	88
$LiCH_2CN$	91
$NaCH(CO_2Me)_2$	89
$NaBH_4$	95 (>39:1)
BH_3	90
CuMe, $AlMe_3$	96 (>39:1)

Rearrangement and Chemospecific Epoxidations. $PhSO_2$CHD-epoxide reacts with alkyl lithium reagents to produce various addition adducts and 3-benzenesulfonyl-cyclohexa-2,4-dienol in modest yield.[7] The conversion was considerably improved by exposing the epoxide to LiHMDS to furnish the dienol in quantitative yield (eq 2). The emergent alkoxide can be protected in situ with *tert*-butyldimethylsilyl chloride in the same yield. Nucleophilic epoxidation of both dienes, protected and



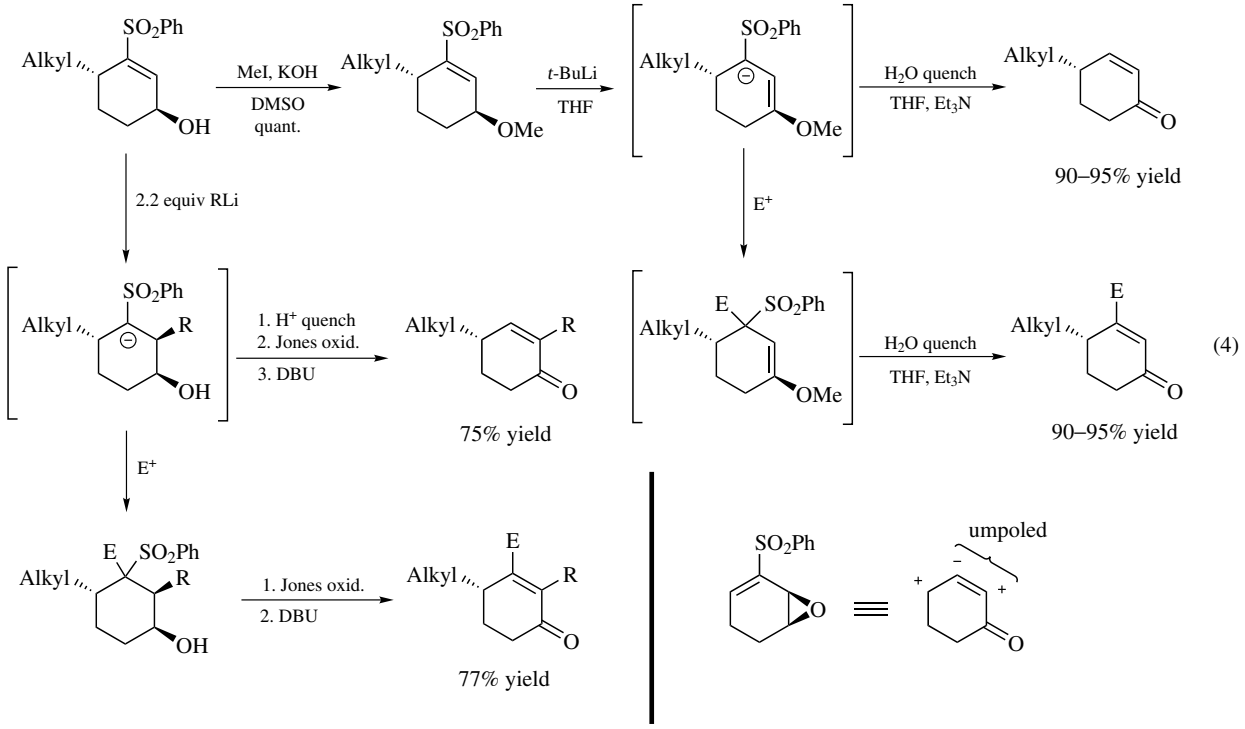
(2)

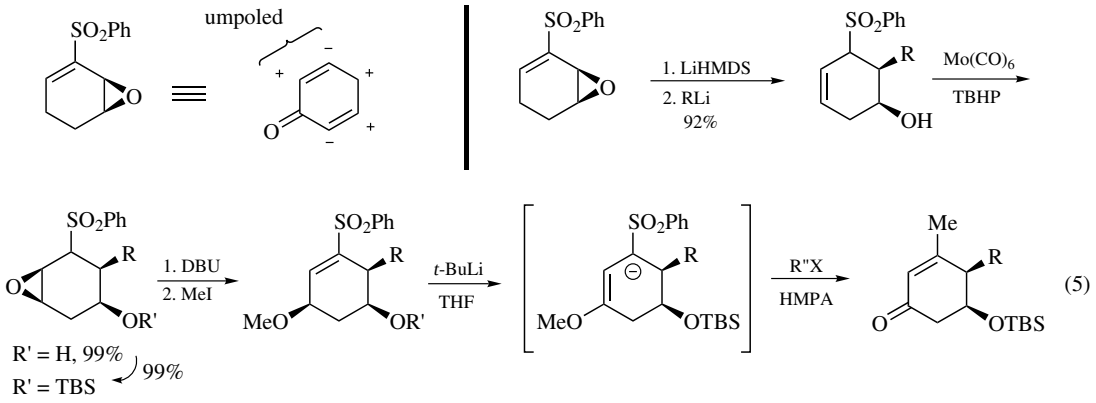


unprotected, produces high yields of *trans* and *cis* epoxides of the vinyl sulfone moiety, respectively. The substituted vinyl epoxides are then capable of undergoing palladium catalyzed additions with various nucleophiles. In the absence of a nucleophile, competing β-hydride elimination occurs to provide di-substituted phenylsulfonyl-1,3-dienes which are analogous to the arene-diols developed by Hudlicky.[3] These reactions are summarized in the article for 2-phenylsulfonyl-1,3-cyclohexadiene.[4]

Second Round of Nucleophilic Addition. Electrophilic epoxidations of 3-benzenesulfonyl-cyclohexa-2,4-dienol, and the protected version, result in stereospecific *cis* and *trans* epoxides from the unconjugated, more electron-rich olefin (eq 3).[5] The substituted vinyl epoxides are then capable of undergoing addition reactions akin to those described above.[4] Very high selectivity can be achieved in the addition reactions as demonstrated by the 1,4-addition of hydride to 5-benzenesulfonyl-7-oxa-bicyclo[4.1.0]hept-4-en-3-ol. The regioselectivity, which translates in this case to enantiomeric excess, is greater than 39:1.[2]

As a 4-Alkyl Enone Scaffold. $PhSO_2CHD$-epoxide can be used as a template for the construction of enantiopure 4-alkyl cyclohex-2-enones (eq 4). Addition of alkyl groups in an exclusive *trans*-1,4-fashion effectively transfers chirality from the epoxide to the newly formed carbon-carbon bond; etherification is quantitative. Isomerization of the γ-methoxy vinyl sulfone to an allylic



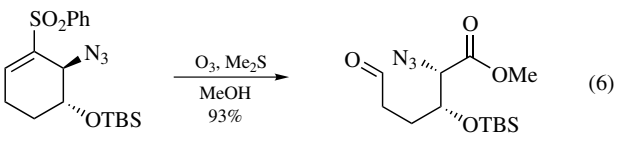


(5)

sulfone with *t*-BuLi followed by basic aqueous work-up provides 4-alkyl cyclohex-2-enones in excellent yield and ee equivalent to the starting $PhSO_2CHD$-epoxide. The isomerized intermediate can be quenched with an electrophile, which, after the same work-up, provides 3-substituted 4-alkyl cyclohex-2-enones.[8] Conjugate addition of 2.2 equiv of an alkyl lithium reagent to the γ-hydroxy vinyl sulfone followed by oxidation and elimination with a base provides 2-substituted 4-alkyl cyclohex-2-enones. Combining the alkyl lithium addition with an electrophilic quench finally provides 2,3-substituted 4-alkyl cyclohex-2-enones after oxidation and elimination.[5] $PhSO_2CHD$-epoxide can therefore be considered as an enantiopure synthon for an umpoled 4-alkyl cyclohex-2-enone.

As a Cyclohexadienone Equivalent. $PhSO_2CHD$-epoxide also can serve as a synthon for differentiated cyclohexa-2,5-dienone equivalents (eq 5). Treatment of $PhSO_2CHD$-epoxide with 1 equiv LiHMDS followed by addition of an alkyl lithium proceeds via sequential γ-metalation/epoxide fragmentation followed by –OLi-directed conjugate addition with quenching at a position α to the sulfone moiety to generate an allylic sulfone. Directed epoxidation and silylation is followed by epoxide elimination with in situ etherification to again provide a γ-methoxy vinyl sulfone. Conversion to the corresponding 3,4,5-trisubstituted cyclohex-2-enone is high yielding and performed as described above.

Oxidative Cleavage. Once the desired stereochemistry is obtained, the phenyl sulfone serves its final purpose during oxidative cleavage using ozone. The immediate product formed is presumably an acyl sulfone which can be converted to an ester (eq 6)[4] or an amide (eq 7).[4] In the absence of an external nucleophile, an internal alcohol can be used to form a lactone (eq 8).[6]



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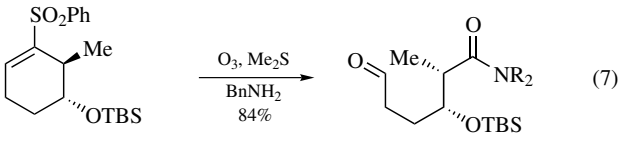
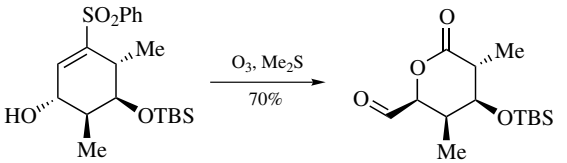


(7)



(8)

1. (a) Fuchs, P. L.; Hentemann, M. F., *Tetrahedron Lett.* **1997**, *38*, 5615. (b) Bäckvall, J.-E.; Juntunen, S. K., *J. Org. Chem.* **1988**, *53*, 2398.
2. Taken from the thesis of Hentemann, M. F. (1998); Evarts, J. (2001); Jiang, W. (2000); Meyers, D. J. (2001), Purdue University, as well as reference 4.
3. (a) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D., *J. Am. Chem. Soc.* **1988**, *110*, 4735. (b) Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T., *J. Am. Chem. Soc.* **1990**, *112*, 9439. (c) Hudlicky, T.; Rouden, J.; Luna, H., *J. Org. Chem.* **1993**, *58*, 985.
4. Fuchs, P. L.; Hentemann, M. F., *Org. Lett.* **1999**, *1*, 355.
5. Fuchs, P. L.; Evarts, J.; Torres, E., *J. Am. Chem. Soc.* **2002**, *124*, 11093.
6. Fuchs, P. L.; Chen, Y.; Evarts, J.; Torres, E., *Org. Lett.* **2002**, *4*, 3571.
7. Saddler, J. C.; Donaldson, R. E.; Fuchs, P. L., *J. Am. Chem. Soc.* **1981**, *103*, 2110–2112.
8. Jin, Z.; Fuchs, P. L., *J. Am. Chem. Soc.* **1994**, *116*, 5995–5996.

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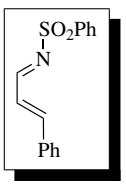
(*E,E*)-*N*-Phenylsulfonyl-4-phenyl-1-aza-1,3-butadiene[1]



[118922-13-7] $C_{15}H_{13}NO_2S$ (MW 271.36)

InChI = 1/C15H13NO2S/c17-19(18,15-11-5-2-6-12-15)16-13-7-10-14-8-3-1-4-9-14/h1-13H/b10-7+,16-13+

InChIKey = FLKIIIPKCJGYIM-NJKRNUQABY

(electron-deficient acyclic 1-azadiene capable of participation in inverse electron demand Diels–Alder reactions with electron-rich dienophiles[2a])

Alternate Name: (*E,E*)-*N*-(3-phenyl-2-propenylidene)benzenesulfonamide.

Physical Data: mp 107–109 °C.

Solubility: sol CH_2Cl_2, C_6H_6.

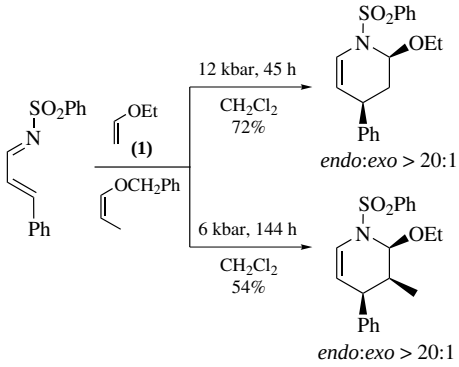
Form Supplied in: pale yellow solid.

Preparative Methods: a solution of cinnamaldehyde in toluene (0.10 M) is treated with benzenesulfonamide (1.1 equiv) and $MgSO_4$ (2 g $mmol^{-1}$) and the reaction mixture is stirred at reflux for 120 h. The reaction mixture is cooled to 25 °C, the $MgSO_4$ is removed by filtration, and the filtrate is concentrated in vacuo. Flash chromatography (SiO_2, 15% EtOAc/hexane eluent) gives the title reagent (typical yield 50%).[2]

Additional general methods for the synthesis of *N*-sulfonylimines based on the in situ generation of *O*-sulfinate derivatives of oximes employing sulfinyl chlorides (phenyl- and methylsulfinyl chloride)[2a,3–8] or sulfonyl cyanides (*p*-toluenesulfonyl cyanide)[2b] and their subsequent rt rearrangement have been detailed.

Handling, Storage, and Precautions: stable at room temperature but susceptible to hydrolysis and must be stored free of moisture.

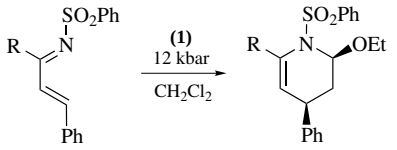
Cycloaddition Reactions. Stable, electron-deficient *N*-(phenylsulfonyl)-1-aza-1,3-butadiene is one of a series of α,β-unsaturated *N*-benzenesulfonyl imines capable of participation in regio- and *endo*-selective inverse electron demand Diels–Alder reactions with a range of electron-rich dienophiles employed in the diastereoselective preparation of substituted *N*-benzenesulfonyl-1,2,3,4-tetrahydropyridines (eq 1).[2a,3]



(1)

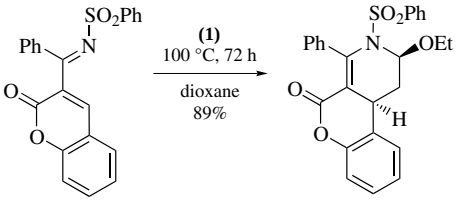
N-Benzenesulfonyl aldimines have been shown to be more reactive than *N*-benzenesulfonyl ketimines (eq 2),[1,2a,3] and the complementary addition of a C-3 or the noncomplementary addition of C-2 and C-4 electron-withdrawing substituents substantially accelerate the Diels–Alder reaction and maintain the expected cycloaddition regioselectivity and exceptionally high *endo* diastereoselectivity (eqs 3–5).[2a,3–5]

Synthetic procedures for preparation of highly substituted or highly functionalized pyridines based on the [4 + 2] cycloaddition reactions of *N*-sulfonyl-1-aza-1,3-butadienes have been developed and their applications in the total syntheses of fredericamycin A (**2**) (eq 6)[6] and streptonigrone (**3**) (eq 7)[7] have been described. The intramolecular [4 + 2] cycloaddition reactions of *N*-sulfonyl-1-aza-1,3-butadienes have been detailed.[8]



(2)

R = CO_2Et > R = H > R = Me > R = Ph



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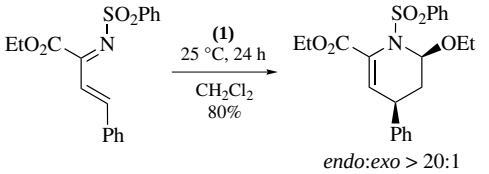

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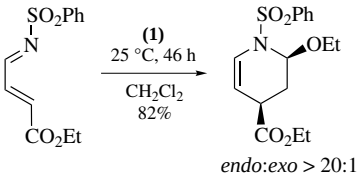

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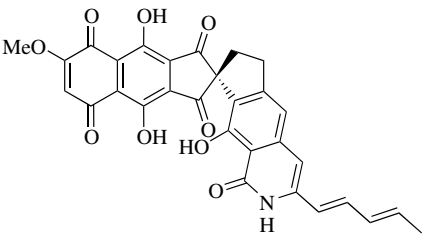
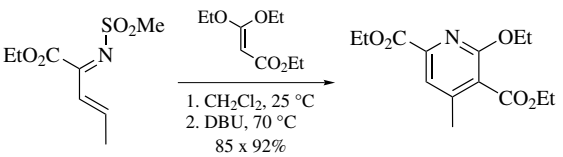


(2) Fredericamycin A



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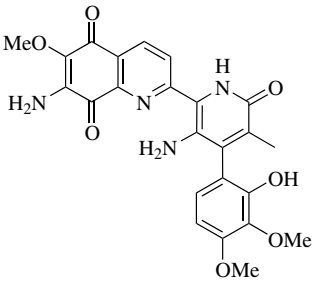
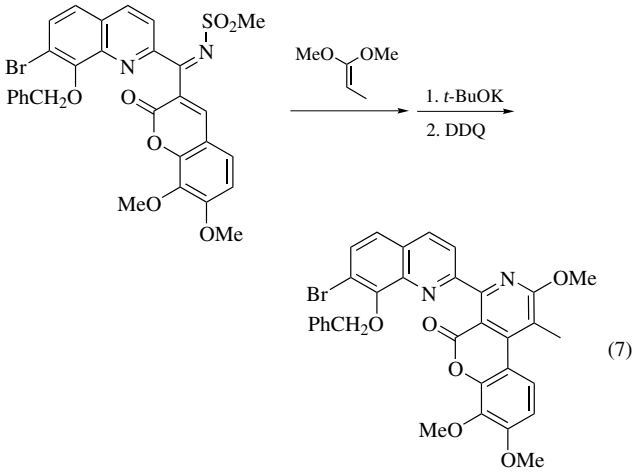


(3) Streptonigrone



(7)

1. Boger, D. L., *Bull. Soc. Chim. Belg.* **1990**, *99*, 599.
2. (a) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M., *J. Am. Chem. Soc.* **1991**, *113*, 1713. (b) Boger, D. L.; Corbett, W. L., *J. Org. Chem.* **1992**, *57*, 4777.
3. Boger, D. L.; Kasper, A. M., *J. Am. Chem. Soc.* **1989**, *111*, 1517.
4. Boger, D. L.; Corbett, W. L.; Wiggins, J. M., *J. Org. Chem.* **1990**, *55*, 2999.
5. Boger, D. L.; Curran, T. T., *J. Org. Chem.* **1990**, *55*, 5349.
6. Boger, D. L.; Zhang, M., *J. Org. Chem.* **1992**, *57*, 3974.
7. Boger, D. L.; Cassidy, K.; Nakahara, K., *J. Am. Chem. Soc.* **1993**, *115*, 10733.
8. Boger, D. L.; Corbett, W. L., *J. Org. Chem.* **1993**, *58*, 2068.

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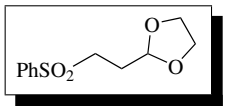
3-(Phenylsulfonyl)propanal Ethylene Acetal



[56161-51-4] $C_{11}H_{14}O_4S$ (MW 242.32)

InChI = 1/C11H14O4S/c12-16(13,10-4-2-1-3-5-10)9-6-11-14-7-8-15-11/h1-5,11H,6-9H2

InChIKey = KKVFFPVBIMFUEZ-UHFFFAOYAP

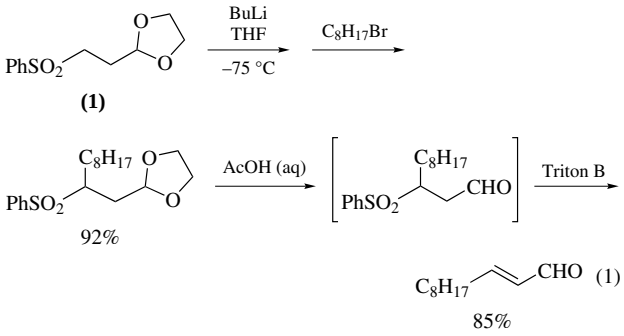
(synthetic reagent for 2-alkenals, 4-oxoalkanals, and 5-hydroxyalkanals)

Physical Data: mp 62–63 °C or 67–68 °C.[1,2]

Form Supplied in: colorless crystals.

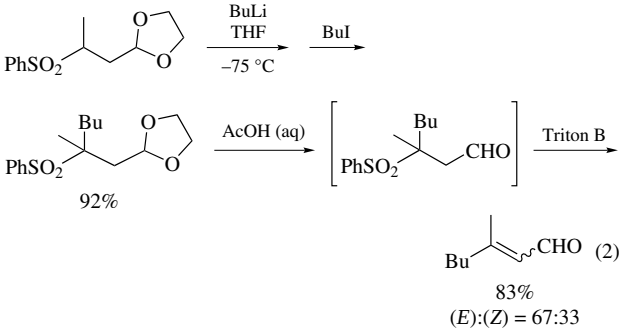
Preparative Methods: by oxidation of 3-(phenylthio)propanal ethylene glycol[1] or by reaction of sodium benzenesulfinate with 3-bromopropanal ethylene acetal.[2]

Synthesis of Alkanals. Monoalkylation of 3-(phenylsulfonyl)propanal ethylene acetal (**1**) takes place at the position α to the phenylsulfonyl group on successive treatment with butyllithium and then with an alkyl halide. Deprotection of the acetal group and subsequent elimination of benzenesulfinic acid with a base produces the corresponding 2-alkenal (eq 1).[1]



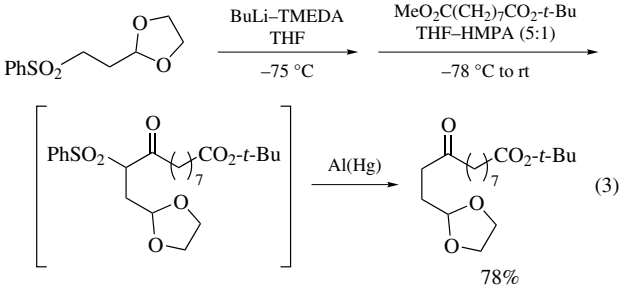
(1)

A second alkylation is also possible by treatment with alkyl iodide and *n*-BuLi. Acidic deprotection of the dialkylated product gives the corresponding 2-alkenal (eq 2).[1]

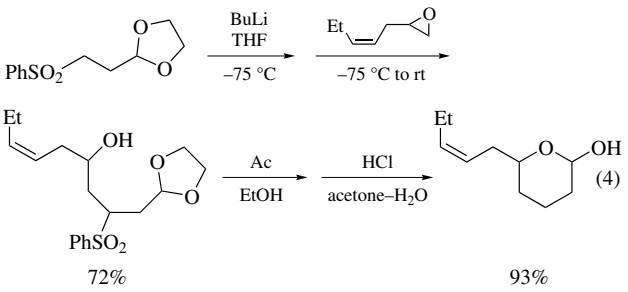


(*E*):(*Z*) = 67:33

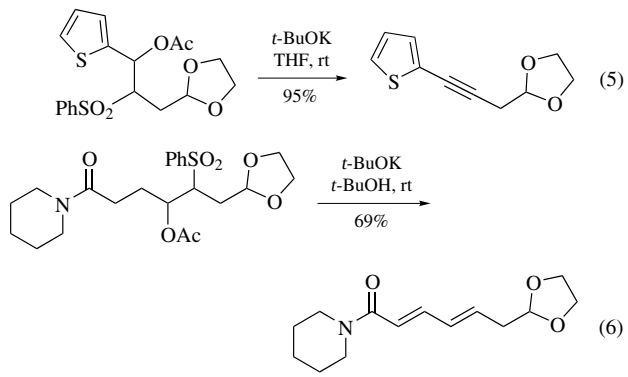
4-Oxoalkanal Synthesis. The lithio derivative of (**1**) can be acylated with a methyl ester to afford an acylated product which easily undergoes reductive desulfurization with aluminum amalgam or sodium amalgam to produce a 4-oxoalkanal ethylene acetal, an important synthetic precursor (eq 3).[3,4]



Synthesis of 5-Hydroxyalkanals. The lithio derivative of (**1**) reacts with terminal epoxides to give ring-opened products. Reductive desulfurization followed by acidic deprotection forms 5-hydroxyalkanal, which cyclizes to give a δ-lactol (eq 4).[5]



Multiple Bond Formation. Lithiated (**1**) adds to aldehydes. After acetylation, treatment of the adduct with potassium *tert*-butoxide causes elimination of benzenesulfinic acid and acetic acid to form an acetal having a triple bond or a conjugated double bond, depending on circumstances (eqs 5 and 6).[6,7]



Related Reagents. 4-Phenylsulfonyl-2-butanone Ethylene Acetal.

1. Kondo, K.; Tunemoto, D., *Tetrahedron Lett.* **1975**, 1007.
2. Gaoni, Y.; Tomazic, A.; Potgieter, E., *J. Org. Chem.* **1985**, *50*, 2943.
3. Kondo, K.; Tunemoto, D., *Tetrahedron Lett.* **1975**, 1397.
4. Menicagli, R.; Wis, M. L.; Lardicci, L.; Botteghi, C.; Caccia, G., *J. Chem. Soc., Perkin Trans. 1* **1979**, 847.
5. Kondo, K.; Saito, E.; Tunemoto, D., *Tetrahedron Lett.* **1975**, 2275.
6. Mandai, T.; Yanagi, T.; Araki, K.; Morisaki, Y.; Kawada, M.; Otera, J., *J. Am. Chem. Soc.* **1984**, *106*, 3670.
7. Mandai, T.; Moriyama, T.; Tsujimoto, K.; Kawada, M.; Otera, J., *Tetrahedron Lett.* **1986**, *27*, 603.

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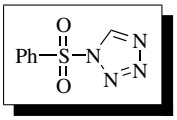
1-Phenylsulfonyl-1*H*-tetrazole



[59128-90-4] $C_7H_6N_4O_2S$ (MW 210.24)

InChI = 1/C7H6N4O2S/c12-14(13,11-6-8-9-10-11)7-4-2-1-3-5-7/h1-6H

InChIKey = YVWCMSOOZISBFJ-UHFFFAOYAO

(coupling reagent for oligonucleotide solution synthesis using the phosphotriester method[1–4])

Physical Data: mp 86–92 °C.

Solubility: insol H_2O; sol pyridine, CH_2Cl_2; reacts slowly with H_2O and protic solvents.

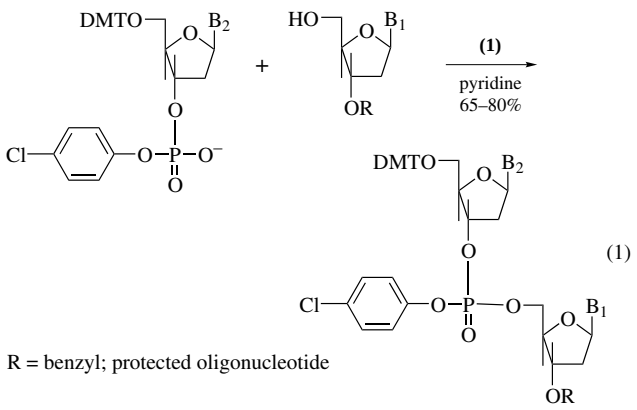
Form Supplied in: white crystals; not available from commercial sources.

Analysis of Reagent Purity: prior to use, the purity should be determined by mp.

Preparative Method: by reaction of benzenesulfonyl chloride (1 equiv) and tetrazole (1 equiv) in the presence of triethylamine (1 equiv) in dioxane at 5 °C for 2 h. A crystalline product was obtained after dissolving the crude material in benzene, shaking with silica gel, filtering, and evaporating in vacuo to dryness.

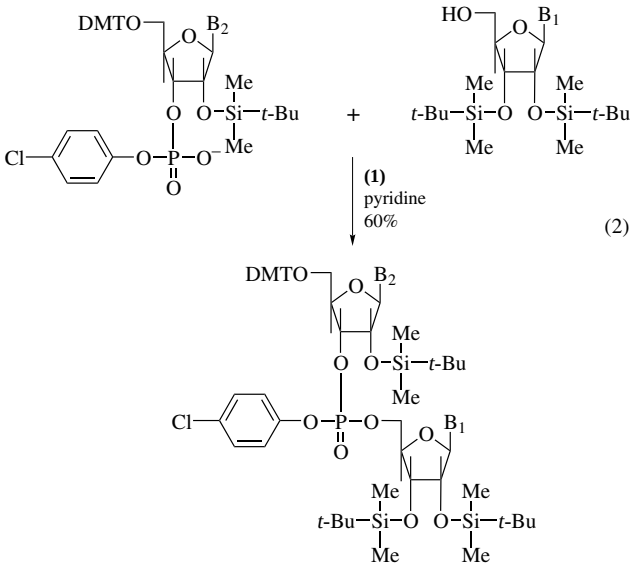
Handling, Storage, and Precautions: the dry solid should be stored in a desiccator with drierite at 4 °C. The material decomposes completely after 20 days at 25 °C, and it should be used immediately following preparation. **Cation**: Avoid contact with metals and metal salts, since tetrazole may form explosive metal salts. Contact with strong oxidizers or strong heat may cause fire or explosion.

1-Phenylsulfonyl-1*H*-tetrazole (**1**) has been used as a condensing reagent in deoxyoligonucleotide solution synthesis by the phosphotriester method.[1–3] It activates 5′-dimethoxytrityl (DMT) deoxynucleoside 3′-(*p*-chorophenyl) phosphates in anhydrous pyridine, allowing the coupling reaction with 5′-hydroxy nucleoside in 30 min at 25 °C, yielding the corresponding *p*-chlorophenyl phosphate dimer in 74% yield. This reaction has been extended for the preparation of oligodeoxynucleotides containing up to 12 bases with coupling times in the range of 30–120 min at 25 °C (eq 1). Couplings mediated by (**1**) occur more rapidly than with



the corresponding 2,4,6-trimethyl and 2,4,6-triisopropyl analogs and no sulfonation at the 5′-hydroxy group has been observed.[1,3]

Furthermore, (**1**) has been used in anhydrous pyridine for 24 h at 25 °C for the preparation of a ribonucleotide dimer in 60% yield (eq 2).



Although (**1**) has not been used in solid-phase oligonucleotide synthesis, another more stable arylsulfonyl derivative, 1-(mesitylsulfonyl)-3-nitro-1,2,4-triazole (MSNT),[5,6] is commonly used in that strategy by the phosphotriester approach.[7]

1. Stawinski, J.; Hozumi, T.; Narang, S. A., *Can. J. Chem.* **1976**, *54*, 670.
2. Stawinski, J.; Hozumi, T.; Narang, S. A.; Bahl, C. P.; Wu, R., *Nucleic Acids Res.* **1977**, *4*, 353.
3. Narang, S. A.; Stawinski, J. U. S. Patent 4 059 592 **1977** (*Chem. Abstr.* **1978**, *88*, 191 349v).
4. Ogilvie, K. K.; Pon, R. T., *Nucleic Acids Res.* **1980**, *8*, 2105.
5. Reese, C. B.; Abasawa, A., *Tetrahedron Lett.* **1980**, *21*, 2265.
6. Tan, Z. K.; Ikuta, S.; Huang, T.; Dugaiczyk, A.; Itakura, K., *Cold Spring Harbor Symp. Quant. Biol.* **1982**, *47*, 383 (*Chem. Abstr.* **1983**, *99*, 22 773a).
7. Itakura, K.; Rossi, J. J.; Wallace, R. B., *Annu. Rev. Biochem.* **1984**, *53*, 323.

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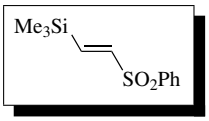
Millipore Corporation, Bedford, MA, USA

(*E*)-1-Phenylsulfonyl-2-trimethylsilylethylene[1]



[64489-06-1] $C_{11}H_{16}O_2SSi$ (MW 240.43)

InChI = 1/C11H16O2SSi/c1-15(2,3)10-9-14(12,13)11-7-5-4-6-8-11/h4-10H,1-3H3/b10-9+

InChIKey = OAFHXIYOGFKWQE-MDZDMXLPBU

(dienophile equivalent to a variety of alkynes in Diels–Alder cycloadditions;[2] used to prepare α-substituted allylsilanes[3])

Physical Data: mp 59–60 °C (petroleum ether).[4]

Solubility: sol common organic solvents.

Form Supplied in: colorless solid; not commercially available.

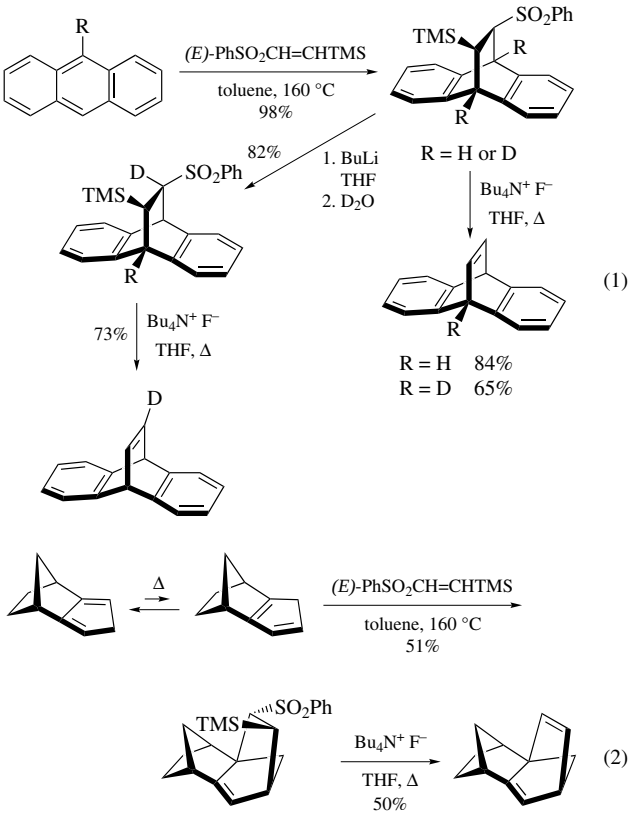
Preparative Methods: prepared by hydrogenation of the corresponding readily available acetylene in 48% yield (this method is also amenable to the synthesis of the deutero derivative)[2] or by phenylsulfonyl chloride addition to trimethylsilylethylene (78%) followed by triethylamine-mediated dehydrochlorination (97%);[2] selenosulfonation, followed by hydrogen peroxide oxidation, can also be used (84%);[5] an alternative method of preparation involves dehydrochlorination of 1-phenylsulfonyl-1-chloro-2-trimethylsilylethane ($PhSO_2CHClCH_2SiMe_3$) with 1,8-diazabicyclo[5.4.0]undec-7-ene (quantitative);[4] can also be prepared by treating the lithium salt of the anion of methylthiomethyl phenyl sulfone ($PhSO_2CH_2SMe$) with (iodomethyl)-trimethylsilane to give $PhSO_2CH(SMe)CH_2SiMe_3$, followed by oxidation to the sulfoxide and elimination of methanesulfenic acid (60%).[3b]

Handling, Storage, and Precautions: potential alkylating agent; use in a fume hood.

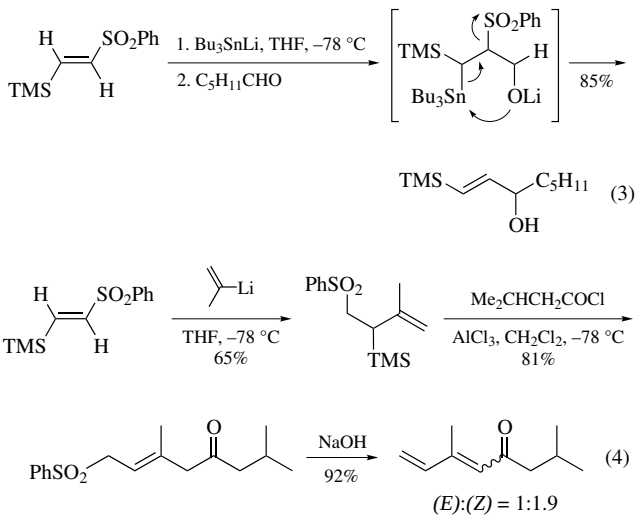
Cycloadditions. The dienophilic properties of (*E*)-phenylsulfonyl-2-trimethylsilylethylene allow the preparation of adducts with reactive dienes such as cyclopentadiene and anthracene.[2] The adducts are smoothly converted to alkenes upon treatment with fluoride ion, establishing the equivalence of the title reagent to acetylene. Alkylation of the α-sulfonyl carbanion can precede the elimination such that synthetic equivalents to HC≡CH, HC≡CD, and RC≡CH are available. The use of this reagent is highlighted by the synthesis of several functionalized dibenzobarrelenes (eq 1).[2] The equivalency to DC≡CD and RC≡CD is illustrated by the preparation of deuterated derivatives.

The somewhat low reactivity of (*E*)-phenylsulfonyl-2-trimethylsilylethylene in Diels–Alder reactions is probably due to steric hindrance exerted by both substituents and by the poor activation imparted by the silyl group. This drawback is partially offset by the effective elimination to the alkene performed under very mild conditions with fluoride ion. The low dienophilic reactivity of the title reagent is evident in the reaction with isodicyclopentadiene, for which it was demonstrated that only the isomer arising from the [1,5]-hydrogen sigmatropic shift was captured by dienophiles of low reactivity. Highly reactive dienophiles react

with the 'symmetric structure', which is obviously a less reactive diene (eq 2).[6]



Addition Reactions. The utility of (*E*)-phenylsulfonyl-2-trimethylsilylethylene in the synthesis of α-substituted allylsilanes[3] is exemplified in eq 3 for γ-hydroxyvinylsilanes,[3a] and in eq 4 in the preparation of isoprenoid structures.[3b] In these reactions the reagent functions as a Michael acceptor, but α-lithiation may compete with less nucleophilic bases such as butyllithium.[3b]



The availability of analogous reagents bearing different atoms in the place of silicon, such as tin,[3] boron,[7a] and chlorine[7b] as well as the alkynic homologs, is notable.[8] Finally, the sulfide related to the title reagent merits mention.[9]

1. Block, E.; Aslam, M., *Tetrahedron* **1988**, *44*, 281.
2. (a) Paquette, L. A.; Williams, R. V., *Tetrahedron Lett.* **1981**, *22*, 4643. (b) Carr, R. V. C.; Williams, R. V.; Paquette, L. A., *J. Org. Chem.* **1983**, *48*, 4976. (c) Paquette, L. A.; Bay, E., *J. Am. Chem. Soc.* **1984**, *106*, 6693.
3. (a) Ochiai, M.; Ukita, T.; Fujita, E., *Tetrahedron Lett.* **1983**, *24*, 4025. (b) Ochiai, M.; Kenzo, S.; Fujita, E.; Tada, S., *Chem. Pharm. Bull.* **1983**, *31*, 3346. (c) Ochiai, M.; Kenzo, S.; Fujita, E., *Chem. Pharm. Bull.* **1984**, *32*, 3686.
4. Hsiao, C.-N.; Shechter, H., *J. Org. Chem.* **1988**, *53*, 2688.
5. (a) Paquette, L. A.; Crouse, G. D., *J. Org. Chem.* **1983**, *48*, 141. (b) Lin, H.-S.; Coghlan, M. J.; Paquette, L. A., *Org. Synth.* **1988**, *67*, 157.
6. Paquette, L. A.; Williams, R. V.; Carr, R. V. C.; Charumilind, P.; Blount, J. F., *J. Org. Chem.* **1982**, *47*, 4566.
7. (a) Martinez-Fresneda, P.; Vaultier, M., *Tetrahedron Lett.* **1989**, *30*, 2929. (b) Montanari, F., *Gazz. Chim. Ital.* **1956**, *86*, 406.
8. (a) Williams, R. V.; Sung, C.-L. A., *J. Chem. Soc., Chem. Commun.* **1987**, 590. (b) Padwa, A.; Wannamaker, M. W., *J. Chem. Soc., Chem. Commun.* **1987**, 1742. (c) Djeghaba, Z.; Jousseaume, B.; Ratier, M.; Duboudin, J.-G., *J. Organomet. Chem.* **1986**, *304*, 115.
9. Magnus, P.; Quagliato, D., *J. Org. Chem.* **1985**, *50*, 1621.

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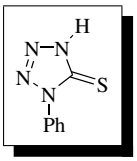
1-Phenyl-2-tetrazoline-5-thione



[86-93-1] $C_7H_6N_4S$ (MW 178.24)

InChI = 1/C7H6N4S/c12-7-8-9-10-11(7)6-4-2-1-3-5-6/h1-5H,(H,8,10,12)/f/h8H

InChIKey = GGZHVNZHFYCSEV-FZOZFQFYCW

(Na salt)

[15052-19-4]

InChI = 1/C7H6N4S.Na/c12-7-8-9-10-11(7)6-4-2-1-3-5-6;/h1-5H,(H,8,10,12);/q;+1/p-1/fC7H5N4S.Na/q-1;m/rC7H5N4NaS/c12-11-7(13)10(8-9-11)6-4-2-1-3-5-6/h1-5H

InChIKey = RSZMKAPXKXEWBY-KCUFNWTOCE

(in combination with isocyanides, activates carboxylate for lactonization,[1] peptide formation;[2] source of nucleophilic sulfur[3])

Physical Data: mp 150 °C (dec).
Solubility: sol organic solvents.
Form Supplied in: red solid; widely available.
Handling, Storage, and Precaution: store in dark.

Original Commentary

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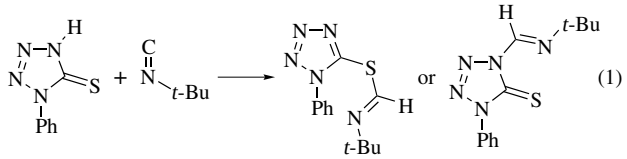
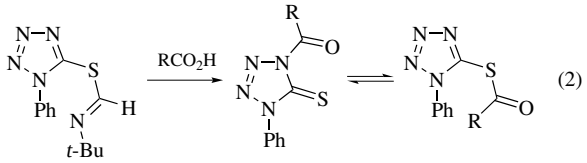
Introduction. While this reagent has a wide variety of applications of great value to the photographic industry, it is also

a synthetic reagent of some utility. These applications relate to activation of the carboxylate group, introduction of nucleophilic sulfur, and as a heterocyclic building block.

Reaction with Isocyanides. Treatment of the reagent with *tert*-butyl isocyanide affords an intermediate of the nature indicated (eq 1). Subsequent reaction with a carboxylic acid at −40 °C gives an equilibrium mixture of compounds (eq 2) in which the carbonyl group is activated toward nucleophilic substitution. This intermediate can be effectively utilized in two ways.

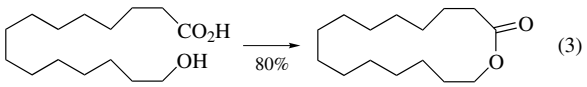


(1)



(2)

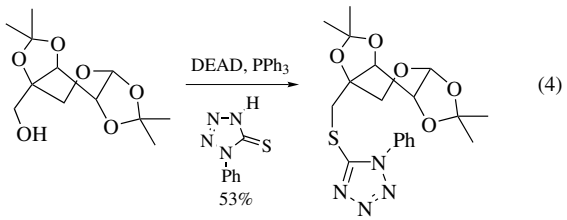
Lactone Formation. Long-chain hydroxy acids can, by this method, be converted into lactones (eq 3).[1] Of note is the observation that even macrocyclic lactones can be formed in high yields without high dilution or other catalysts.



(3)

Peptide Formation. Amino acids can be coupled to form amides using this technology.[2] A nitrogen-protected amino acid is activated and allowed to react with a carboxylate-protected amino acid, thus forming the peptide linkage. The reagent can be recovered unchanged at the end of either of these sequences.

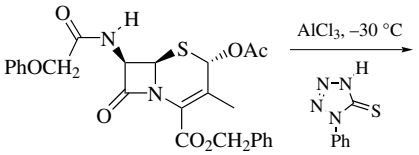
Sulfur Nucleophile. The nucleophilic nature of the sulfur in 1-phenyl-2-tetrazoline-5-thione can be utilized for the introduction of sulfur into organic compounds. Thus Mitsunobu reaction of a protected sugar with the reagent affords the substituted sugar (eq 4).[3]

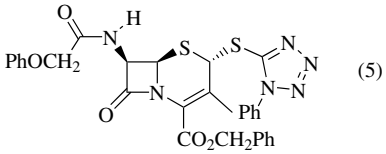


(4)

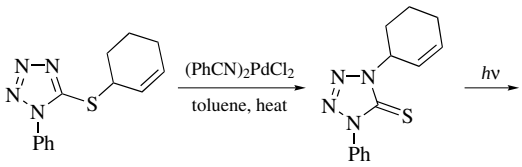
In a similar fashion, substitution of a cephalosporin could be achieved (eq 5).[4]

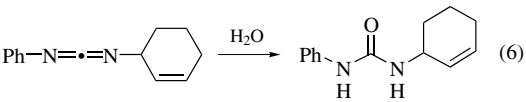
Alkylation at nitrogen (or redirected to nitrogen) affords the substituted tetrazolinethione. Under photolysis conditions, such compounds undergo loss of sulfur and nitrogen to afford the carbodiimide (eq 6),[5] subsequent hydrolysis providing the urea.





(5)





(6)

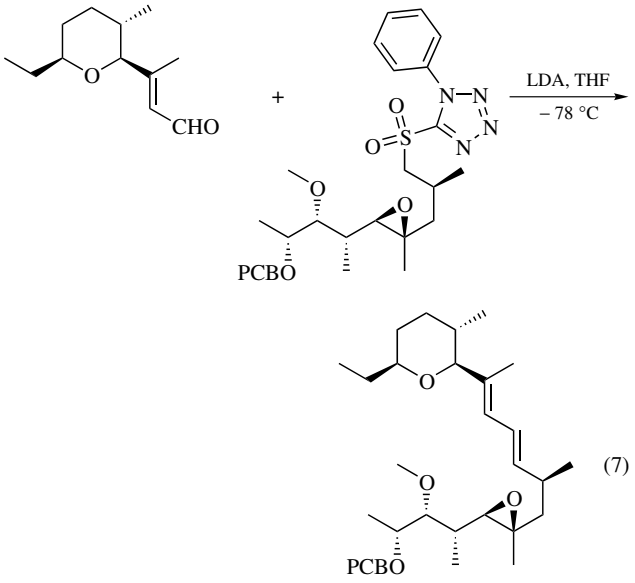
First Update

Milan Bruncko
Abbott Laboratories, Abbott Park, IL, USA

Olefination. One of the most important applications of alkyl-2-sulfonyl-1-phenyl-1*H*-tetrazoles, formed by nucleophilic displacement of a suitable leaving group by 1-phenyl-2-tetrazoline-5-thione followed by sulfur oxidation, is the Kocienski-Julia-type olefination reaction that is extensively used in the synthesis of many natural products. Alkenes formed in this manner are produced with excellent *E*-stereoselectivities and in high yields. The *E*/*Z* ratio is influenced by choice of both polarity and coordinating ability of the solvent (increases from DME>THF>Et_2O>toluene), and by counter ion (K>Na>Li).[6] For example, Kocienski and coworkers utilized this methodology in a key step involving coupling of two herboxidiene fragments (eq 7).[7]

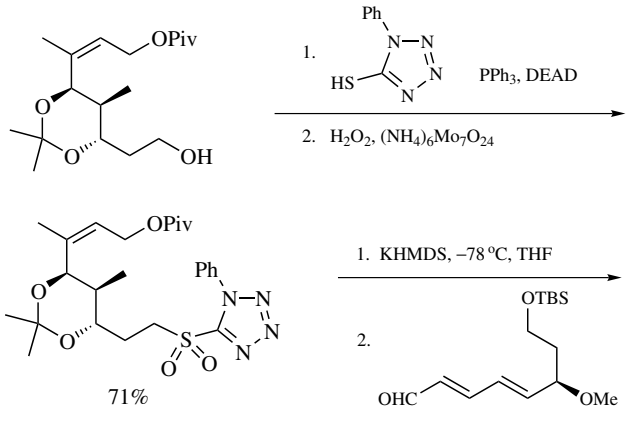
In a further example, Smith and Wan exploited the nucleophilic capability of 1-phenyl-2-tetrazoline-5-thione in the Mitsunobu reaction, followed by oxidation to the sulfone with hydrogen peroxide and ammonium heptamolybdate tetrahydrate as a key step in a synthesis of the ansamycin antiobiotic, (+)-thiazinotrienomycin-E (eq 8).[8] Importantly, use of the phenyltetrazolylthione-derived sulfone gave an *E*/*Z* ratio of 10:1 in this coupling whereas the more conventional benzthiazole-2-thiol-derived system resulted in a selectivity of only 1.5:1 in favor of the *E*-isomer.

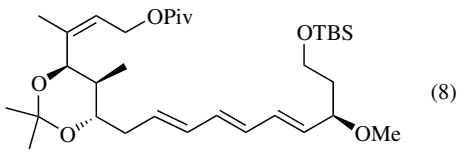
Suzuki Coupling. 1-Phenyl-2-tetrazolyl-5-thioethers have been employed in modified Suzuki couplings when they serve as donors of the phenyltetrazolyl moiety. The coupling of the thioether and a boronic acid was catalyzed by Pd_2dba_3 /tris(2-furanyl)phosphine with assistance of 1.2 equiv of Cu(I)-thiophene-2-carboxylate (eq 9).[9]



(7)

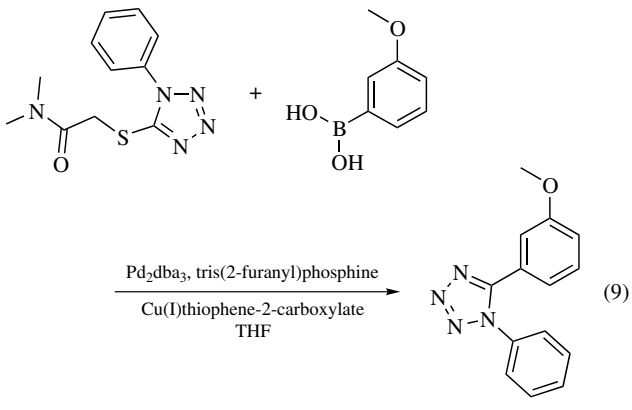
81% (*E*/*Z* 91:9)





(8)

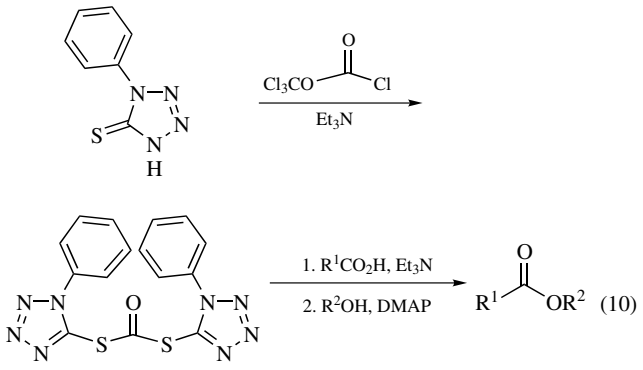
85% (*E*/*Z* 10:1)



(9)

64%

Esterification. Treatment of 1-phenyl-2-tetrazoline-5-thione with trichloromethyl chloroformate forms the symmetrical dithiocarbonate. This stable, crystalline solid acts as a novel reagent for the one-pot esterification of acids (eq 10).

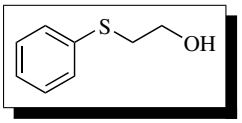


(10)

Related Reagents. Benzthiazole-2-thiol; 1-*tert*-Butyl-1*H*-2-tetrazoline-5-thione.

1. Schmidt, U.; Dietsche, M., *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 771.
2. Schmidt, U.; Dietsche, M., *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 143.
3. Besson, T.; Neirabeyeh, M. A.; Viaud, M. C.; Rollin, P., *Synth. Commun.* **1990**, *20*, 1631.
4. Torii, S.; Tanaka, H.; Saitoh, N.; Siroi, T.; Sasaoka, M.; Tada, N.; Nokami, J., *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2185.
5. Quast, H.; Nahr, U., *Chem. Ber.* **1985**, *118*, 526.
6. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A., *Synlett* **1998**, 26.
7. Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K., *J. Chem. Soc., Perkin Trans. 1* **1999**, 955.
8. Smith, A. B.; Wan, Z., *J. Org.Chem.* **2000**, *65*, 3738.
9. Liebeskind, L. S.; Srogl, *J., Org. Lett.* **2002**, *4*, 979.
10. Takeda, K.; Tsuboyama, K.; Takayanagi, H.; Ogura, H., *Synthesis* **1987**, 560.

2-Phenylthioethanol

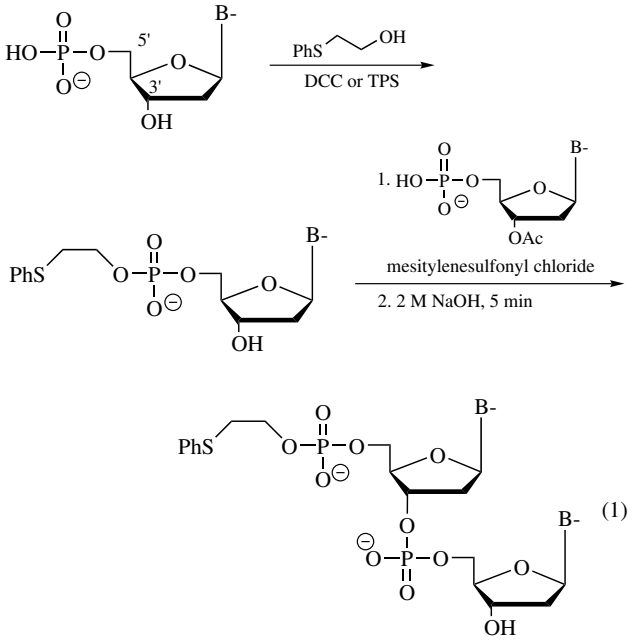


[699-12-7] $C_8H_{10}OS$ (MW 154.23)
InChI = 1/C8H10OS/c9-6-7-10-8-4-2-1-3-5-8/h1-5,9H,6-7H2
InChIKey = KWWZHCSQVRVQGF-UHFFFAOYAL

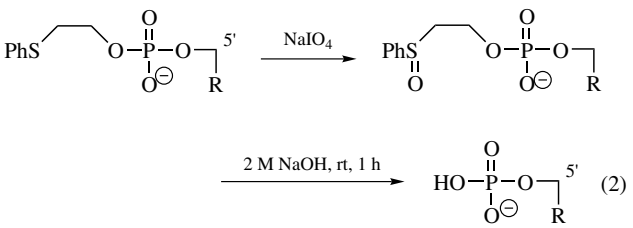
(reagent used as a protecting agent in nucleotide synthesis)

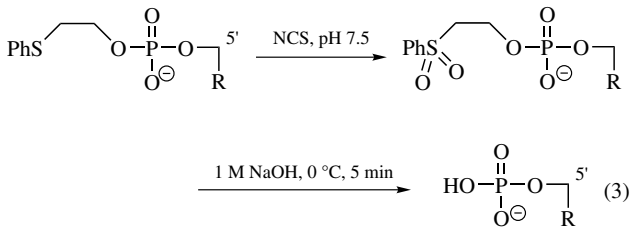
Alternate Name: 2-phenylmercaptoethanol.
Physical Data: bp 115–116 °C/ 2 mm Hg, density 1.14 g cm^{-3}; mp 57–58 °C (as 4-nitrobenzoate ester).
Form Supplied in: stench liquid; commercially available.
Preparative Methods: prepared by the reaction of thiophenol with ethylene chlorohydrin in 20% NaOH aqueous solution.[1]
Handling, Storage, and Precaution: toxicity and other health hazards are not reported.

Phosphate Protecting Group in Oligonucleotide Synthesis. Protection of phosphates is particularly important in the synthesis of oligonucleotides. The commonly used protecting group is 2-cyanoethyl, which is introduced to a phosphate with 2-cyanoethanol and DCC/pyridine and can be cleaved by aqueous ammonia. In automated oligonucleotide synthesis, 2-cyanoethyl repeatedly protects and deprotects the 3′-phosphate at each condensation step in high yields. When condensation starts with the 5′-phosphate nucleotide, the phosphate protecting group must resist all the condensation processes, including deprotection of 3′-OH and amino groups. 2-Phenylthioethanol is employed for such a protection.[2] Protection of the deoxymononucleotide 5′-phosphate is accomplished by treating its pyridinium salt with 2-phenylthioethanol and DCC. The protection can also be performed with triisopropylbenzenesulfonyl chloride (TPS). Condensation with a second nucleotide and succeeding condensations do not touch the protected 5′-phosphate of the terminal nucleotide (eq 1). The phosphate protected by 2-phenylthioethanol is stable under 1 M aqueous NaOH, concentrated ammonium hydroxide at 50 °C, and aqueous HCl at pH 2 at room temperature.



Deprotection of the 5′-phosphate is easily accomplished after oxidative treatment. Oxidation with sodium metaperiodate in water (or in 0.1 M triethylammonium bicarbonate) gives the corresponding sulfoxide derivative. The free nucleotide is liberated by treatment with 2 M aqueous sodium hydroxide at room temperature (eq 2). Alternatively, the sulfide is oxidized to sulfone with NCS in 0.1 M triethylammonium bicarbonate buffer at room temperature. In this case, deprotection can be achieved successfully under milder conditions involving 1 M aqueous sodium hydroxide at 0 °C for 5 min (eq 3).[3]





1. Ford-Moore, A. H.; Peters, R. A.; Wakelin, R. W., *J. Chem. Soc.* **1949**, 1754.
2. (a) Narang, S. A.; Bhanot, O. S.; Goodchild, J.; Wightman, R. H.; Dheer, S. K., *J. Am. Chem. Soc.* **1972**, *94*, 6183. (b) Wightman, R. H.; Narang, S. A.; Itakura, K., *Can. J. Chem.* **1972**, *50*, 456. (c) Narang, S. A.; Itakura, K.; Bahl, C. P.; Katagiri, N., *J. Am. Chem. Soc.* **1974**, *96*, 7074.
3. Agarwal, K. L.; Fridkin, M.; Jay, E.; Khorana, H. G., *J. Am. Chem. Soc.* **1973**, *95*, 2020.

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(Phenylthio)nitromethane[1]

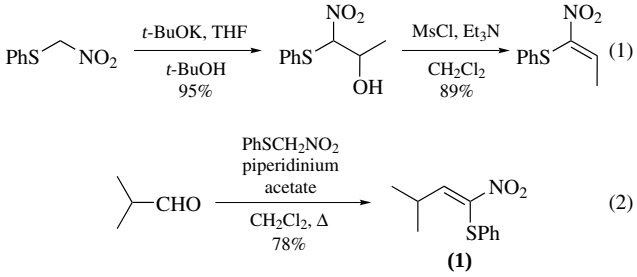
[60595-16-6] $C_7H_7NO_2S$ (MW 169.22)
InChI = 1/C7H7NO2S/c9-8(10)6-11-7-4-2-1-3-5-7/h1-5H,6H2
InChIKey = GJGUOMBYPKDBSS-UHFFFAOYAA

(precursor for 1-nitro-1-phenylthioalkenes,[2] furans,[3] bicyclic β-lactams,[4] and amino acids[5])

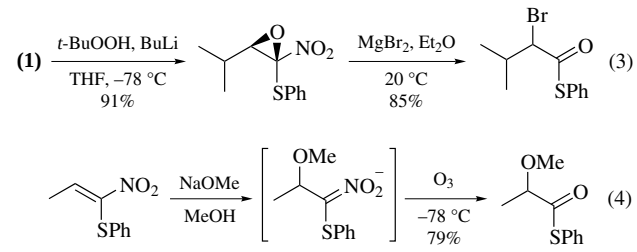
Alternate Name: nitro(phenylthio)methane.
Physical Data: bp 85–95 °C/0.05 mmHg;[6] n_D^{23} 1.5785;[7] pK_a (DMSO) 11.9.[7]
Solubility: insol cold H_2O; sol CH_2Cl_2, benzene, THF.
Analysis of Reagent Purity: ^{1}H NMR: 5.45 (s, 2H) and 7.25–7.5 ppm (m, 5H).[6]
Preparative Method: most conveniently prepared by reaction of the sodium salt of nitromethane with benzenesulfenyl chloride.[6,8]
Handling, Storage, and Precautions: may be stored essentially unchanged in a freezer at −25 °C; unpleasant odor; best handled in a well-ventilated hood; any spillage may be cleaned up with commercial bleach.

Nitroalkene Synthesis. Henry reaction of (phenylthio)nitromethane with aldehydes followed by dehydration has been used to prepare (*Z*)-1-nitro-1-phenylthioalkenes.[2–5] potassium *tert*-butoxide-catalyzed addition and dehydration via mesylation (eq 1), or direct condensation catalyzed by piperidinium acetate (eq 2),[9] are the methods of choice. Henry reaction can be also carried out by reaction of the nitroalkene dianion with aldehydes.[8–11]

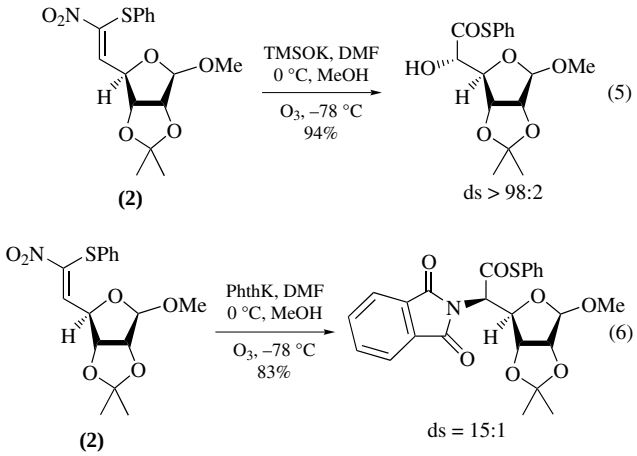
The adducts of cyclic ketones and (phenylthio)nitromethane undergo ring expansion to provide 2-(phenylthio)cycloalkanones on aluminum chloride-mediated denitration.[11]



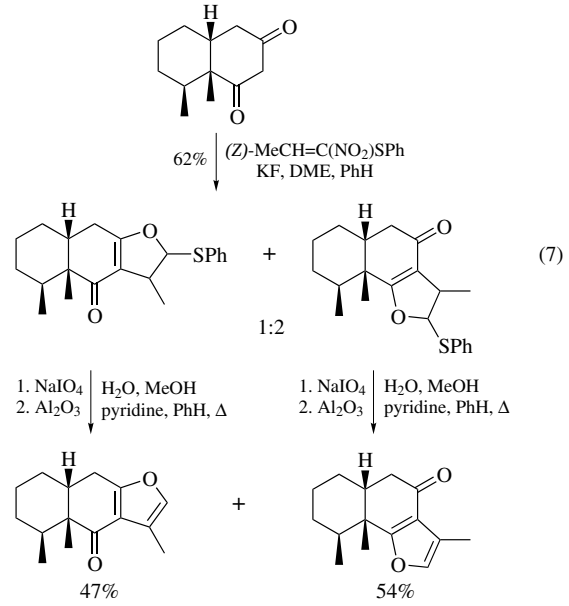
1-Nitro-1-phenylthioalkenes (**1**), on reaction with *tert*-butyl hydroperoxide, are converted into epoxides and these species react with nucleophiles (halide salts, boron trifluoride etherate, trifluoroacetic acid, MsOH) to provide α-substituted phenylthio esters (eq 3).[9] Alternatively, Michael addition of nucleophiles (alkoxides, $Phth^-$, Ts^-, malonate) to 1-nitro-1-phenylthioalkenes and ozonolysis of the intermediate nitronate gave similar adducts (eq 4), including α-amino and α-hydroxy acid derivatives.[2]



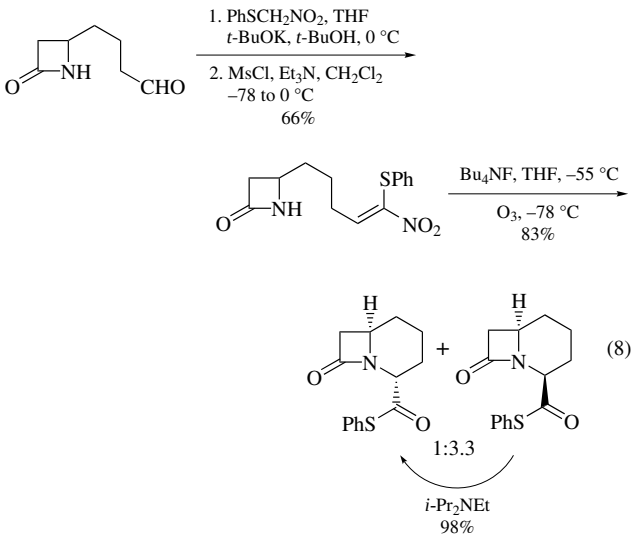
(Phenylthio)nitromethane is useful in polyoxin synthesis.[5,12] A ribose nitroalkene (**2**), derived from (phenylthio)nitromethane and the corresponding aldehyde (93%), was found to react with opposite stereochemical biases with potassium trimethylsilanoate (eq 5) and phthalimide (eq 6) followed by ozonolysis. The hydroxy acid (eq 5) was further transformed into polyoxin C.

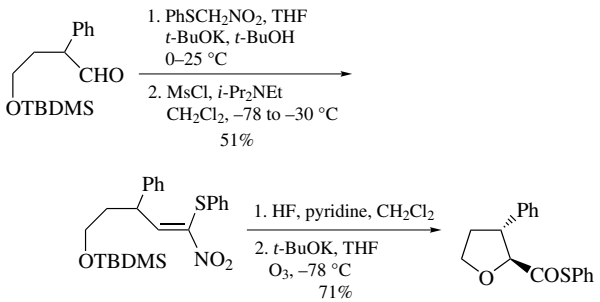


Synthesis of Heterocycles. 1-Nitro-1-phenylthiopropene is an excellent reagent for the synthesis of furanoterpenoids.[3,13] Condensation with β-diketones and sulfoxide elimination gave ligularone and isoligularone, respectively (eq 7). The methods were also used to prepare curzerenone, epicurzerenone, and pyrocurzerenone.

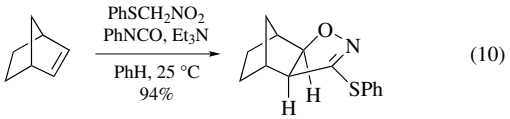


Nitroalkenes derived from β-lactam aldehydes may be converted into diverse bicyclic β-lactams via intramolecular Michael addition and ozonolysis (eq 8). The method is appropriate for penam, carbapenam, carbacephem, and oxapenam arrays.[4] In some cases, (benzyloxy)nitromethane is a superior reagent.[14] This Michael addition–oxidation strategy is also useful for the synthesis of tetrahydrofuran (eq 9) and -pyran systems.[15]

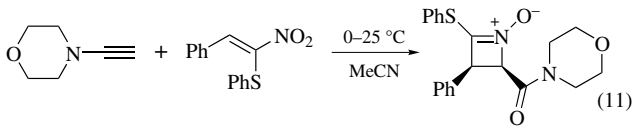




(Phenylthio)nitromethane has been dehydrated and the resultant phenylthionitrile oxide trapped with alkenes to provide isoxazolines (eq 10).[16] These compounds are convenient precursors for 3-(phenylsulfonyl)isoxazolines and β-hydroxy ketones. The cycloaddition–ring contraction of ynamines with 1-nitro-1-phenylthioalkenes has been used to prepare cyclic nitrones (eq 11).[17]

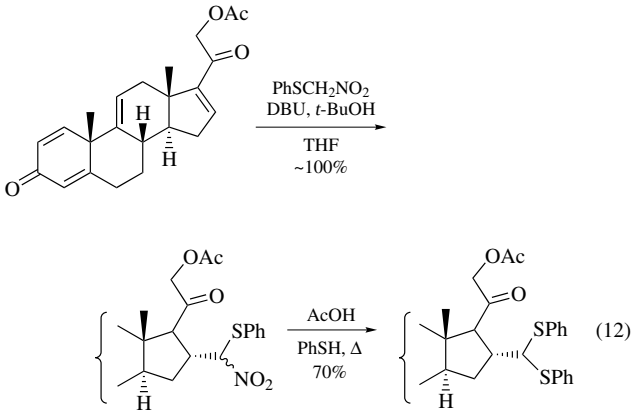


(10)



(11)

The Michael addition of (phenylthio)nitromethane to a steroidal enone and nitro displacement (eq 12) has been employed in the stereoselective 16-methylation of corticosteroids.[18]



(12)

1. Barrett, A. G. M., *Chem. Soc. Rev.* **1991**, *20*, 95.
2. (a) Barrett, A. G. M.; Graboski, G. G.; Russell, M. A., *J. Org. Chem.* **1986**, *51*, 1012. (b) Banks, B. J.; Barrett, A. G. M.; Russell, M. A., *J. Chem. Soc., Chem. Commun.* **1984**, 670.
3. (a) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A., *J. Org. Chem.* **1980**, *45*, 2945. (b) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A., *J. Chem. Soc., Chem. Commun.* **1978**, 362.
4. (a) Barrett, A. G. M.; Graboski, G. G.; Sabat, M.; Taylor, S. J., *J. Org. Chem.* **1987**, *52*, 4693. (b) Barrett, A. G. M.; Graboski, G. G.; Russell, M. A., *J. Org. Chem.* **1985**, *50*, 2603.
5. Barrett, A. G. M.; Lebold, S. A., *J. Org. Chem.* **1990**, *55*, 3853.
6. Barrett, A. G. M.; Dhanak, D.; Graboski, G. G.; Taylor, S. J., *Org. Synth.* **1989**, *68*, 8.
7. (a) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Druker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S., *J. Org. Chem.* **1977**, *42*, 326. (b) Bordwell, F. G.; Bartmess, J. E., *J. Org. Chem.* **1978**, *43*, 3101.
8. Seebach, D.; Lehr, F., *Helv. Chim. Acta* **1979**, *62*, 2239.
9. (a) Ashwell, M.; Jackson, R. F. W., *J. Chem. Soc., Chem. Commun.* **1988**, 282. (b) Ashwell, M.; Jackson, R. F. W.; Kirk, J. M.; *Tetrahedron* **1990**, *46*, 7429.
10. Lehr, F.; Gonnermann, J.; Seebach, D., *Helv. Chim. Acta* **1979**, *62*, 2258.
11. Kim, S.; Park, J. H., *Chem. Lett.* **1988**, 1323.
12. Barrett, A. G. M.; Weipert, P. D.; Dhanak, D.; Husa, R. K.; Lebold, S. A., *J. Am. Chem. Soc.* **1991**, *113*, 9820.
13. (a) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A., *Tennen Yuki Kago Butsu Toronki Koen Yoshishu* **1978**, *21*, 472 (*Chem. Abstr.* **1979**, *90*, 168 757j). (b) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A., *J. Org. Chem.* **1984**, *49*, 3728. (c) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A., *Chem. Lett.* **1981**, 593; **1979**, 163.
14. (a) Barrett, A. G. M.; Cheng, M.-C.; Spilling, C. D.; Taylor, S. J., *J. Org. Chem.* **1989**, *54*, 992. (b) Barrett, A. G. M.; Cheng, M.-C.; Sakdarat, S.; Spilling, C. D.; Taylor, S. J., *Tetrahedron Lett.* **1989**, *30*, 2349. (c) Barrett, A. G. M.; Sakdarat, S., *J. Org. Chem.* **1990**, *55*, 5110.
15. Barrett, A. G. M.; Flygare, J. A.; Spilling, C. D., *J. Org. Chem.* **1989**, *54*, 4723.
16. (a) Curran, D. P.; Chao, J.-C., *J. Org. Chem.* **1988**, *53*, 5369. (b) Harada, K.; Kaji, E.; Zen, S., *Nippon Kagaku Kaishi* **1981**, 1195.
17. Van Eijk, P. J. S. S.; Overkempe, C.; Trompenaars, W. P.; Reinhoudt, D. N.; Manninen, L. M.; VanHummel, G. J.; Harkema, S., *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 27.
18. Boivin, J.; Chauvet, C.; Zard, S. Z., *Tetrahedron Lett.* **1992**, *33*, 4913.

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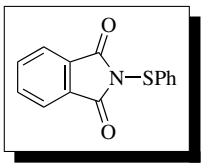
N-Phenylthiophthalimide[1]

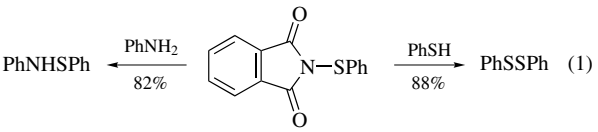


[14204-27-4] $C_{14}H_9NO_2S$ (MW 255.31)
InChI = 1/C14H9NO2S/c16-13-11-8-4-5-9-12(11)14(17)15(13)18-10-6-2-1-3-7-10/h1-9H
InChIKey = NMHKBABHRKQHOL-UHFFFAOYAF

(mild sulfenylating reagent)

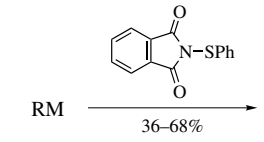
Physical Data: mp 160–161 °C; colorless solid.
Preparative Method: by reaction of benzenesulfenyl chloride with phthalimide in the presence of triethylamine.[1]

General Discussion. *N*-Phenylthiophthalimide has been shown to be a mild sulfenylating reagent that is useful for a range of synthetic applications. This reagent reacts with amines[2] and thiols[3] to give the corresponding sulfenyl amines and disulfides respectively (eq 1).



(1)

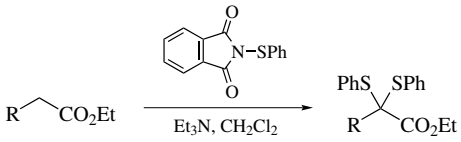
Upon reaction with Grignard reagents or organolithium compounds, mixed sulfides are formed (eq 2).[4]



(2)

M = MgBr, Li

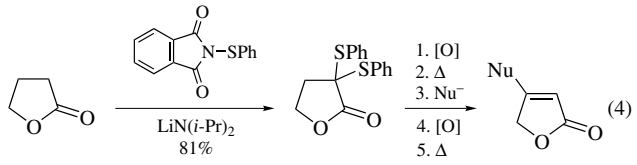
Activated carbonyl compounds can be cleanly bis-sulfenylated by this reagent in the presence of Et_3N (eq 3).[5]



(3)

R = CO_2Et, 94%; MeCO, 93%

Bis-sulfenylation of γ-butyrolactone, as well as of cyclic ketones, has been achieved with this reagent via the corresponding lithium enolates.[6] This reaction has been utilized in an efficient synthesis of 3-substituted 2-buten-4-olides (eq 4).



(4)

1. Behforouz, M.; Kerwood, J. E., *J. Org. Chem.* **1969**, *34*, 51.
2. Harpp, D. N.; Back, T. G., *Tetrahedron Lett.* **1971**, *12*, 4953.
3. Boustany, K. S.; Sullivan, A. B., *Tetrahedron Lett.* **1970**, *11*, 3547.
4. Furukawa, M.; Suda, T.; Hayashi, S., *Synthesis* **1974**, 282.
5. Grossert, J. S.; Dubey, P. K., *J. Chem. Soc., Chem. Commun.* **1982**, 1183.
6. Watanabe, M.; Shirai, K.; Kumamoto, T., *Nippon Kagaku Kaishi* **1982**, 1780.

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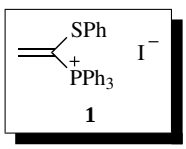
1-Phenylthiovinyl Triphenylphosphonium Iodide



1

[69442-52-0] $C_{26}H_{22}IPS$ (MW 524.40)

InChI = 1/C26H22PS.HI/c1-22(28-26-20-12-5-13-21-26)27(23-14-6-2-7-15-23,24-16-8-3-9-17-24)25-18-10-4-11-19-25;/h2-21H,1H2;1H/q+1;/p-1/fC26H22PS.I/h;1h/qm;-1

InChIKey = BJPSYGCZHLDZOE-LKFHSSDACZ

(reagent used as a two-carbon component in intramolecular Wittig reactions)

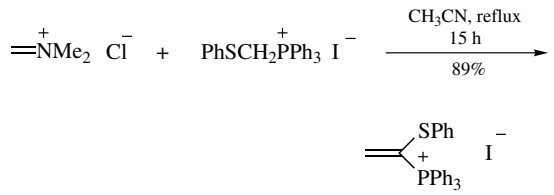
Physical Data: mp 145–146 °C.

Solubility: soluble in dichloromethane, chloroform, and acetonitrile.

Form Supplied in: pale yellow crystalline solid.

Analysis of Reagent Purity: NMR, microanalysis.

Preparative Methods: can be prepared from (phenylthiomethyl) triphenylphosphonium iodide and *N*,*N*-dimethylmethylene ammonium chloride in refluxing acetonitrile (eq 1).[2]

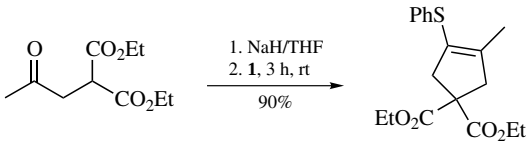


(1)

Purity: recrystallization from acetonitrile/ethyl acetate.

Handling, Storage, and Precautions: stable to prolonged storage in dry conditions; decomposed by aqueous base.

Preparation of Cyclopentane Derivatives. The vinyl phosphonium salt (**1**) reacts with carbon-centered nucleophiles, in compounds which contain a suitable ketone functionality, to give a cyclopentene. Generally this represents an extension of the chemistry originally developed by Schweizer with triphenylvinylphosphonium bromide.[1] The advantages of using **1** rather than vinyltriphenylphosphonium bromide are that the yields in comparable reactions tend to be higher, presumably because the phenylthio substituent increases the Michael acceptor ability of the reagent and/or stabilizes the intermediate ylide, and that the product is a vinyl sulfide, which has potential for further development to other useful compounds such as ketones (by hydrolysis) and vinyl sulphones (by oxidation). Thus **1** has been used to prepare cyclopentenes such as **2** (eq 2),[2] the dithiane derivative **3** (eq 3),[2] which was used in the development of a synthesis of PGD_1,[3] and the bicyclo[3.3.0]octenes **4** (eq 4)[4] and **5** (eq 5)[5] used, respectively, in the synthesis of hirsutene and pentalenolactone.



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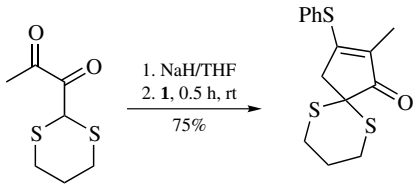
(2)



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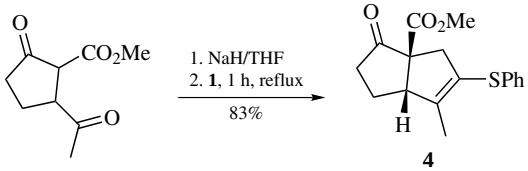
(3)



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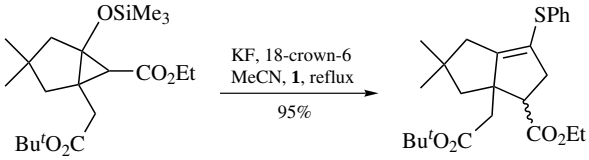
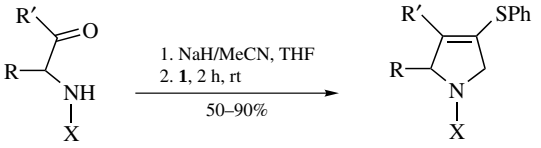
(4)



(5)

5

Preparation of Pyrrolidine Derivatives. In a manner analogous to that described above, the use of appropriately functionalized nitrogen-centered nucleophiles allows the preparation of nitrogen heterocycles. Thus the *N*-benzoyl or *N*-phenylsulphonyl derivatives (**6**) of α-aminoketones, readily prepared from α-amino acids, react with **1** under basic conditions to give the 2,5-dihydropyrrole (**7**) (eq 6). Product **7** may be modified to provide variously substituted pyrroles.[6,7] Use of homochiral ketone derivative **6** allows essentially complete retention of configuration to provide **7** as a single enantiomer.[8]

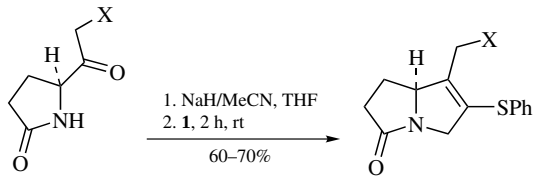


(6)

6 **7**

X = COPh or SO_2Ph

5-Acyl-2-pyrrolidine derivatives (**8**) undergo cyclization with **1** to provide pyrrolizidines (**9**), again with retention of configuration (eq 7).[9]

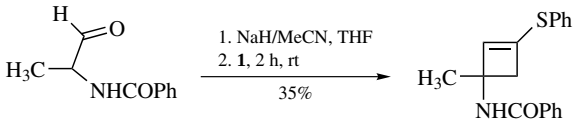


(7)

8 **9**

X = H or OAc

A single example is described using an α-amino aldehyde derivative where the product was not the expected 2,5-dihydropyrrole but was the cyclobutene (**10**), although the yield was lower (eq 8).[7] This change in the course of reaction probably reflects a subtle alteration in the relative acidities of the α-proton and the NH proton in changing from a ketone to an aldehyde.



(8)

10

Related Reagents. Triphenylvinylphosphonium Bromide;[1] 1-(Methylthiovinyl)triphenylphosphonium Chloride;[2] 1-(Methylthiovinyl)triphenylphosphonium Tetrafluoroborate;[2] Diphenyl (1-phenylthiovinyl)phosphine Oxide;[10] (+)-(*S*)-Diethoxyphosphorylvinyl *p*-Tolyl Sulfoxide.[11]

1. Schweizer, E. E.; Wehman, A. T.; Nycz, D. M., *J. Org. Chem.* **1973**, *38*, 1583.
2. Cameron, A. G.; Hewson, A. T., *J. Chem. Soc., Perkin Trans. 1* **1983**, 2979.
3. Cameron, A. G.; Hewson, A. T.; Wadsworth, A. H., *J. Chem. Soc., Perkin Trans. 1* **1984**, 2337.
4. Hewson, A. T.; Macpherson, D. T., *J. Chem. Soc., Perkin Trans. 1* **1985**, 2625.
5. Marino, J. P.; Silveira, G.; Comasseto, J.; Petragnani, N., *J. Org. Chem.* **1987**, *52*, 4139.
6. Burley, I.; Hewson, A. T., *Synthesis* **1995**, 1151.
7. Burley, I.; Bilic, B.; Hewson, A. T.; Newton, J. R. A., *Tetrahedron Lett.* **2000**, *41*, 8969.
8. Burley, I.; Hewson, A. T., *Tetrahedron Lett.* **1994**, *35*, 7099.
9. Boynton, C. M.; Hewson, A. T.; Mitchell, D., *J. Chem. Soc., Perkin Trans. 1* **2000**, 3599.
10. Grayson, J. I.; Warren, S.; Zaslona, A. T., *J. Chem. Soc., Perkin Trans. 1* **1987**, 967.
11. Mikolajczyk, M.; Midura, W. H., *Tetrahedron: Asymmetry* **1992**, *3*, 1515.

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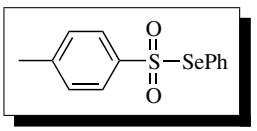
Se-Phenyl *p*-Tolueneselenosulfonate[1]



[68819-94-3] $C_{13}H_{12}O_2SSe$ (MW 311.28)

InChI = 1/C13H12O2SSe/c1-11-7-9-12(10-8-11)16(14,15)17-13-5-3-2-4-6-13/h2-10H,1H3

InChIKey = RTBHXKLOGIHSJF-UHFFFAOYAM

Physical Data: mp 79.5–80 °C.

Solubility: soluble in chloroform, dichloromethane, THF, and benzene.

Form Supplied in: yellow, crystalline, odorless solid.

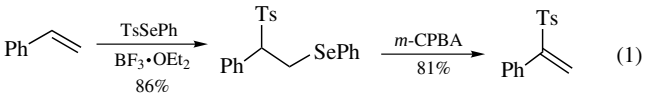
Preparative Methods: add *p*-toluenesulfonhydrazide in methanol dropwise to an equimolar amount of benzeneseleninic acid in methanol at 0 °C; cool at −5 °C overnight, filter the highly pure crystalline selenosulfonate (96% yield);[2] alternatively, use 2 equiv of *p*-toluenesulfinic acid[3] instead of *p*-toluenesulfonhydrazide; several other preparative methods are also available;[4] *Se*-phenyl benzeneselenosulfonate can be prepared in the same way and can be used similarly for most purposes.

Purity: recrystallization from methanol (unnecessary when prepared as recommended above).

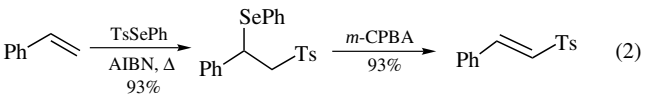
Handling, Storage, and Precaution: routine handling is possible, but avoid prolonged exposure to light and heat; store in the dark at 0 °C; may be toxic; use in a fume hood and avoid skin contact.

Selenosulfonation of Alkenes, Allenes, and Dienes. The 1,2-additions of the selenosulfonate to unsaturated substrates are known as selenosulfonations.[5] Alkenes react under either Lewis-acid-catalyzed (eq 1) or free-radical conditions (eq 2). The former reactions proceed stereospecifically (anti) and regioselectively (Markovnikov),[5] whereas the latter are nonstereospecific

chain processes and afford the opposite regiochemistry (anti-Markovnikov).[3,5] Free-radical additions may be initiated photochemically[3,6] or by heating with AIBN[5] in solvents such as benzene, chloroform or carbon tetrachloride. A ruthenium(II)-mediated photoaddition has been reported to be especially useful for electron-rich alkenes (eq 3).[7] Selenoxide *syn*-elimination of the adducts can be effected with *m*-CPBA or hydrogen peroxide, affording high yields of the corresponding vinyl sulfones,[3,5,6] which were in turn investigated as dienophiles in various Diels–Alder reactions.[8] Applications have been reported in the synthesis of sterpuric acid[8b] and hirsutene.[8c] A polystyrene-supported version of the selenosulfonate, attached to the polymer via the selenium moiety, has also been used in both the Lewis-acid-catalyzed and thermally initiated selenosulfonation protocols.[9]



(1)



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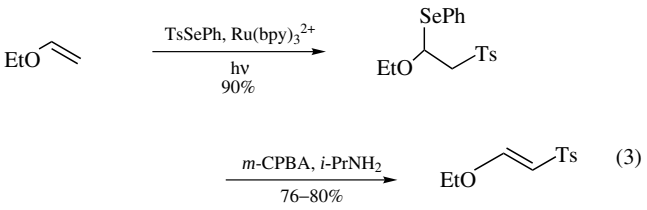
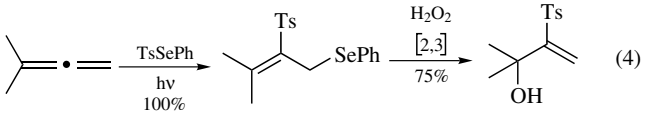


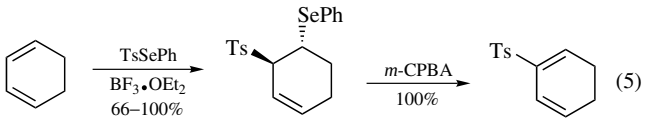
(3)

Allenes undergo free-radical selenosulfonation with regioselective incorporation of the sulfonyl moiety at the central allenic carbon atom, producing 2-sulfonyl allylic alcohols after oxidation and [2,3]sigmatropic rearrangement of the corresponding selenoxides (eq 4).[10]



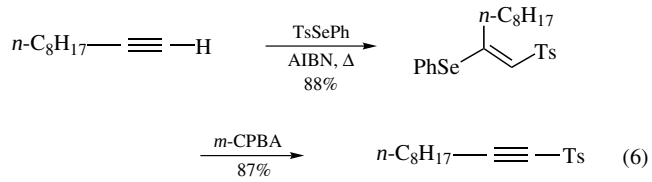
(4)

Conjugated dienes react with the selenosulfonate in the presence of boron trifluoride etherate to afford the corresponding 1,2-adducts, which produce 2-sulfonyl-1,3-dienes after selenoxide elimination (eq 5).[5,11] Cycloheptatriene produced the corresponding 2-sulfonylcycloheptatriene derivative in 57% overall yield upon similar selenosulfonation and selenoxide elimination.[12]

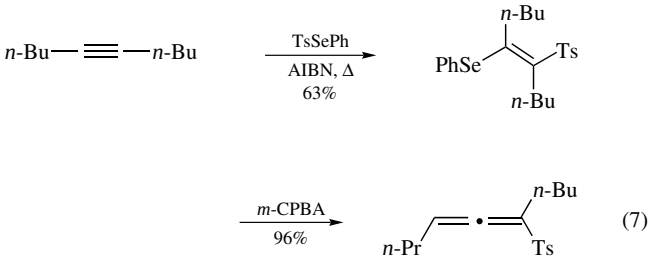


(5)

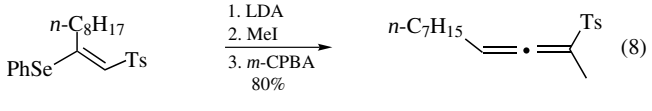
Selenosulfonation of Alkynes and Enynes. The free-radical selenosulfonation of alkynes proceeds via anti addition with anti-Markovnikov regiochemistry. Subsequent selenoxide eliminations produce acetylenic and allenic sulfones from terminal and internal alkynes, respectively (eqs 6 and 7).[13] The 1,2-adducts can also be γ-deprotonated and alkylated in the α-position, resulting in the formation of the corresponding allylic sulfones. Selenoxide elimination of the latter compounds thus provides access to substituted allenic sulfones from terminal alkynes (eq 8).[14] An enantioselective variation of this process based on asymmetric selenoxide eliminations in the last step has been reported.[15] The 1,2-adducts or their selenoxides react with nucleophiles by addition-elimination or elimination-addition processes to give the products of overall substitution of the selenium residue (eq 9). Possible nucleophiles include organocuprates, alcohols, amines, cyanide, active methylene compounds, lithiated dithianes, and propargylic anions.[13a,16] These protocols have been applied to the synthesis of the side chains of marine sterols[17] and brassinosteroids.[18] Acetylenic sulfones obtained via selenosulfonation react with amines containing pendant chloroalkyl or ester substituents to form various nitrogen heterocycles (eq 10), which have in turn been converted into dendrobatid alkaloids and related products.[19]



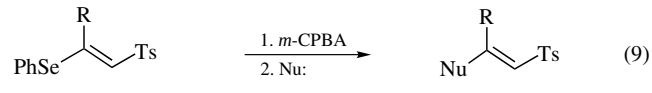
(6)



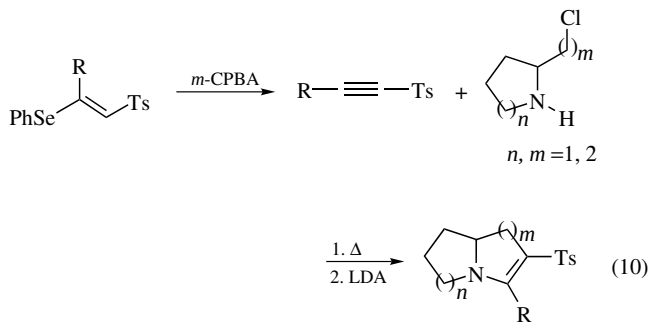
(7)



(8)



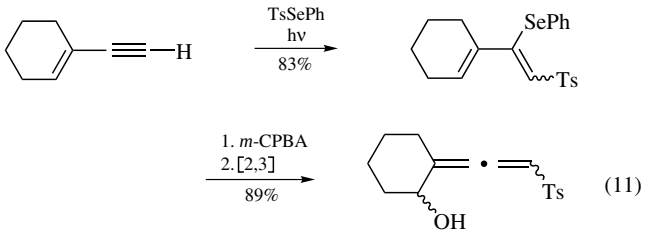
(9)

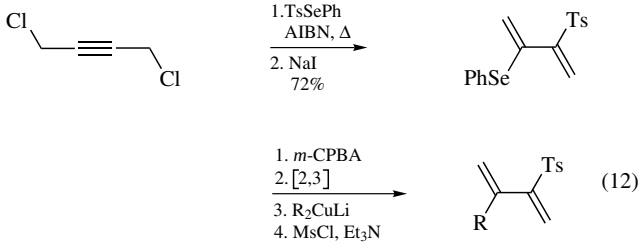


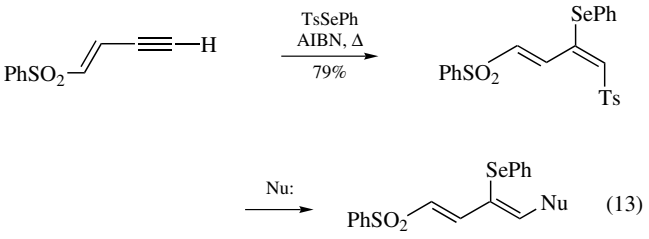
(10)

Enynes with terminal alkyne moieties cleanly afford the products of 1,2-addition to the triple bond (eq 11), but more highly substituted derivatives and those containing terminal alkene groups

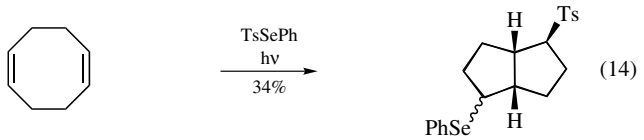
give more complex mixtures containing the products of addition to the double bond, as well as 1,4-adducts. Products such as the example in eq 11 afford allenic alcohols after oxidation and [2,3]sigmatropic rearrangement.[20] The selenosulfonation of 1,4-dichloro-2-butyne can be followed by reductive dehalogenation to afford the corresponding 2,3-adduct, thereby regenerating a unit of unsaturation and making the starting material function as an enyne equivalent. The 2,3-adduct can then be converted into various 3-substituted 2-sulfonyl-1,3-dienes as shown in eq 12.[20] The selenosulfonation of 1-sulfonylenynes affords adducts that undergo substitutions with Grignard reagents or heteroatom nucleophiles, as shown in eq 13.[21]

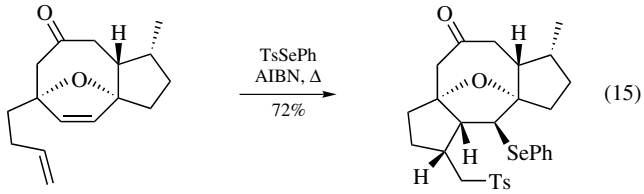


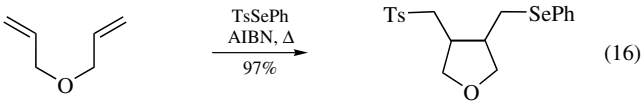


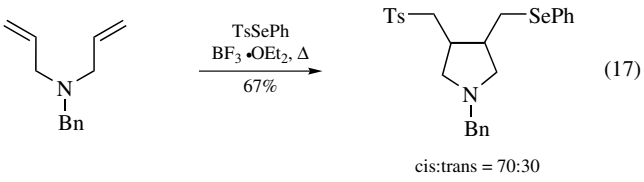


Radical Cyclizations. Several examples of radical cyclizations have been reported during the selenosulfonation of cyclic[3] or acyclic dienes.[22] When the tether linking the two alkene moieties includes a heteroatom, the procedure affords the corresponding heterocycles.[22b,22c,22f] Illustrative examples are shown in eqs 14–17.[3,22d,22b,22f] In eq 17, quaternization of the nitrogen atom with a Lewis acid affects the yield and stereochemistry of the radical cyclization. Similar cyclizations occur when unconjugated enynes[22c] or bisallenes[23] are subjected to selenosulfonation.

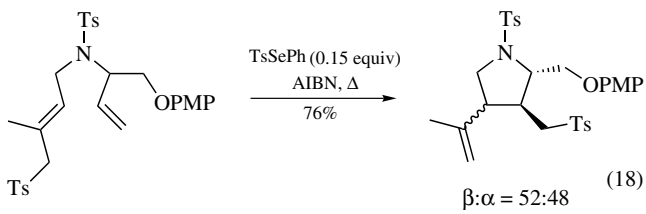


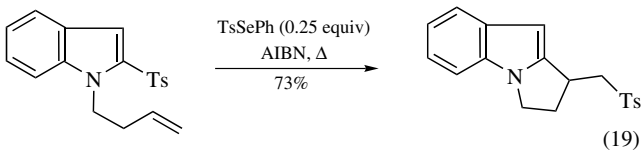




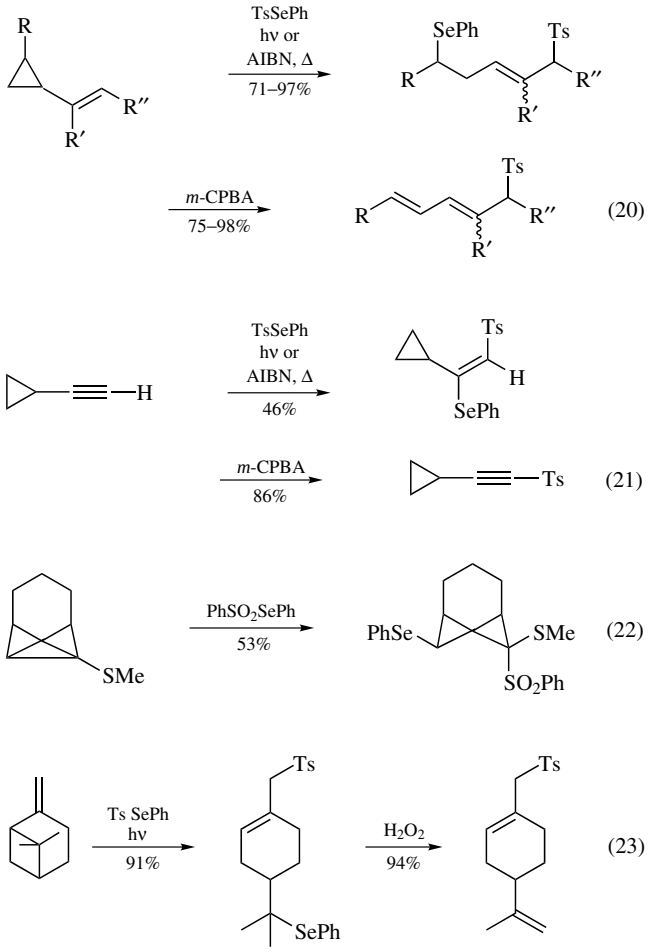


When one of the alkene units of the diene is replaced by an allyl sulfone moiety, cyclization may be initiated with a smaller than stoichiometric amount of the selenosulfonate, since displacement of a sulfonyl radical from the allyl sulfone group propagates the chain reaction (eq 18).[22f,24] A related procedure that leads to the cyclization of sulfonyl-substituted indoles is shown in eq 19.[25]





Selenosulfonation of Compounds with Small Rings. The free-radical selenosulfonation of vinylcyclopropanes is accompanied by ring-opening to give 1,5-addition products that afford 1-sulfonyl-2,4-dienes by selenoxide elimination (eq 20).[26] Similar ring-opening is observed in cyclopropylidenes, whereas cyclopropylacetylene undergoes mainly 1,2-addition and provides the corresponding acetylenic sulfone after selenoxide elimination (eq 21).[26] The tricyclo[4.1.0.$0^{2,7}$]heptane in eq 22 underwent ring-opening even at room temperature,[27] while β-pinene was similarly cleaved under photochemical conditions (eq 23).[22a]



Miscellaneous Reactions. The reactions of the selenosulfonate with acyl derivatives of *N*-hydroxy-2-thiopyridone,[28] alkyl, alkenyl, and alkynyl derivatives of tin and mercury;[29] triethylgermane[30] and diazomethane[31] have also been reported, but the synthetic potential of these processes remains to be determined.

Related Reagents. Benzeneselenenyl Bromide; Benzeneselenenyl Chloride; Benzeneselenenyl Trifluoromethanesulfonate; Diphenyl Diselenide; *N*-Phenylselenophthalimide; *Se*-Phenyl Trifluoromethaneselenosulfonate.

1. (a) Back, T. G., In *Organoselenium Chemistry – A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999, p. 105 and 176. (b) Simpkins, N. S., *Sulphones in Organic Synthesis*; Pergamon: Oxford, 1993, p 22, 45, 82. (c) Back, T. G., *Phosphorus, Sulfur, and Silicon* **1992**, *67*, 203. (d) Back, T. G.; Brunner, K.; Krishna, M. V.; Lai, E. K. Y; Muralidharan, K. R., In *Heteroatom Chemistry*; Block, E., Ed.; VCH: New York, 1990, Chap 4, p 79.
2. Back, T. G.; Collins, S.; Krishna, M. V., *Can. J. Chem.* **1987**, *65*, 38.
3. Gancarz, R. A.; Kice, J. L., *J. Org. Chem.* **1981**, *46*, 4899.
4. (a) Wang, L.; Huang, X., *Synth. Commun.* **1993**, *23*, 2817. (b) Chen, D.-W.; Chen, Z.-C., *Tetrahedron Lett.* **1994**, *35*, 7637.
5. Back, T. G.; Collins, S., *J. Org. Chem.* **1981**, *46*, 3249.
6. Lin, H.-S.; Coghlan, J.; Paquette, L. A., *Org. Synth.* **1989**, *67*, 157.
7. Barton, D. H. R.; Csiba, M. A.; Jaszberenyi, J. C., *Tetrahedron Lett.* **1994**, *35*, 2869.
8. (a) Kinney, W. A.; Crouse, G. D.; Paquette, L. A., *J. Org. Chem.* **1983**, *48*, 4986. (b) Paquette, L. A.; Lin, H.-S.; Gunn, B. P.; Coghlan, M. J., *J. Am. Chem. Soc.* **1988**, *110*, 5818. (c) Moriarty, K. J.; Shen, C.-C.; Paquette, L. A., *Synlett* **1990**, 263. (d) Martin, M. G. G.; Horton, D., *Carbohydrate Res.* **1989**, *191*, 223. (e) Black, K. A.; Vogel, P., *J. Org. Chem.* **1986**, *51*, 5341.
9. Qian, H.; Huang, X., *Synlett* **2001**, 1913.
10. Kice, J. L.; Kang, Y. -H., *Tetrahedron* **1985**, *41*, 4739.
11. (a) Bäckvall, J.-E.; Nájera, C; Yus, M., *Tetrahedron Lett.* **1988**, *29*, 1445. (b) Plobeck, N. A.; Bäckvall, J.-E., *J. Org. Chem.* **1991**, *56*, 4508.
12. Tong, Z.; Chen, Y.; Hentemann, M. F.; Fuchs, P. L., *Tetrahedron Lett.* **2000**, *41*, 7795.
13. (a) Back, T. G.; Collins, S.; Kerr, R. G., *J. Org. Chem.* **1983**, *48*, 3077. (b) Back, T. G.; Collins, S.; Gokhale, U.; Law, K.-W., *J. Org. Chem.* **1983**, *48*, 4776. (c) Miura, T.; Kobayashi, M., *J. Chem. Soc., Chem. Commun.* **1982**, 438.
14. Back, T. G.; Krishna, M. V.; Muralidharan, K. R., *J. Org. Chem.* **1989**, *54*, 4146.
15. Komatsu, N.; Murakami, T.; Nishibayashi, Y.; Sugita, T.; Uemura, S., *J. Org. Chem.* **1993**, *58*, 3697.
16. (a) Back, T. G.; Collins, S.; Law, K.-W., *Can. J. Chem.* **1985**, *63*, 2313. (b) Back, T. G.; Krishna, M. V., *J. Org. Chem.* **1987**, *52*, 4265. (c) Back, T. G.; Collins, S.; Krishna, M. V.; Law, K.-W., *J. Org. Chem.* **1987**, *52*, 4258.
17. Back, T. G.; Proudfoot, J. R.; Djerassi, C., *Tetrahedron Lett.* **1986**, *27*, 2187.
18. Back, T. G.; Krishna, M. V., *J. Org. Chem.* **1991**, *56*, 454.
19. (a) Back, T. G.; Nakajima, K., *J. Org. Chem.* **1998**, *63*, 6566. (b) Back, T. G.; Nakajima, K., *J. Org. Chem.* **2000**, *65*, 4543.
20. Back, T. G.; Lai, E. K. Y.; Muralidharan, K. R., *J. Org. Chem.* **1990**, *55*, 4595.
21. Yoshimatsu, M.; Hayashi, M.; Tanabe, G.; Muraoka, O., *Tetrahedron Lett.* **1996**, *37*, 4161.
22. (a) Kang, Y.-H.; Kice, J. L., *J. Org. Chem.* **1984**, *49*, 1507. (b) Chuang, C.-P., *Synth. Commun.* **1992**, *22*, 3151. (c) Brumwell, J. E.; Simpkins, N. S.; Terrett, N. K., *Tetrahedron* **1994**, *50*, 13533. (d) Blake, A. J.; Highton, A. J.; Majid, T. N.; Simpkins, N. S., *Org. Lett.* **1999**, *1*, 1787. (e) Gutierrez-Avella, D.-M.; Bertrand, M.; Nouguier, R., *C.R. Acad. Sci. Paris, Chimie* **2001**, *4*, 453. (f) Bertrand, M.-P.; Gastaldi, S.; Nouguier, R., *Tetrahedron* **1998**, *54*, 12829.
23. Kang, S.-K.; Ha, Y.-H.; Kim, D.-H.; Lim, Y.; Jung, J., *J. Chem. Soc., Chem. Commun.* **2001**, 1306.
24. Bertrand, M.-P.; Gastaldi, S.; Nouguier, R., *Tetrahedron Lett.* **1996**, *37*, 1229.
25. Caddick, S.; Shering, C. L.; Wadman, S. N., *Tetrahedron* **2000**, *56*, 465.
26. Back, T. G.; Muralidharan, K. R., *J. Org. Chem.* **1989**, *54*, 121.
27. Vasin, V. A.; Kostryukov, S. G.; Razin, V. V., *Russian J. Org. Chem.* **1999**, *35*, 1616.
28. Barton, D. H. R.; Ramesh, M., *Tetrahedron Lett.* **1990**, *31*, 949.
29. (a) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. I.; Pla-Dalmau, A.; Khanna, R. K., *J. Am. Chem. Soc.* **1988**, *110*, 3530. (b) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H.; Hershberger, J., *Organometallics* **1987**, *6*, 1414.
30. Kobayashi, M.; Kobayashi, M.; Yoshida, M., *Bull. Chem. Soc. Jpn.* **1985**, *58*, 473.
31. Back, T. G., *J. Org. Chem.* **1981**, *46*, 5443.

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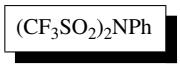
N-Phenyltrifluoromethanesulfonimide[1]



[37595-74-7] $C_8H_5F_6NO_4S_2$ (MW 357.28)

InChI = 1/C8H5F6NO4S2/c9-7(10,11)20(16,17)15(6-4-2-1-3-5-6)21(18,19)8(12,13)14/h1-5H

InChIKey = DIOHEXPTUTVCNX-UHFFFAOYAA

(mild triflating agent[2] for amine protection;[3,4] vinyl triflate formation from thermodynamic[2] and kinetic enolates[5] generated by deprotonation, conjugate reduction,[6,7] or conjugate addition;[7] formation of aryl triflates[2])

Alternate Names: *N*-phenyltriflimide; Hendrickson–McMurray reagent.[6]

Physical Data: mp 101–103 °C (Aldrich), 93–94 °C.[2]

Form Supplied in: white solid; widely available.

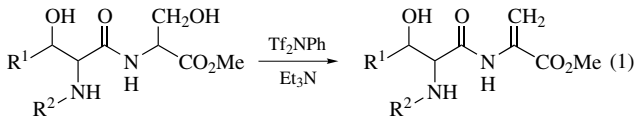
Preparative Methods: prepared in 92% yield from the reaction of aniline with 2 equiv each of trifluoromethanesulfonic anhydride and triethylamine in CH_2Cl_2 at −78 °C.[2]

Handling, Storage, and Precautions: nonhygroscopic and extremely stable.

Original Commentary

Wayne E. Zeller
Illinois State University, Normal, IL, USA

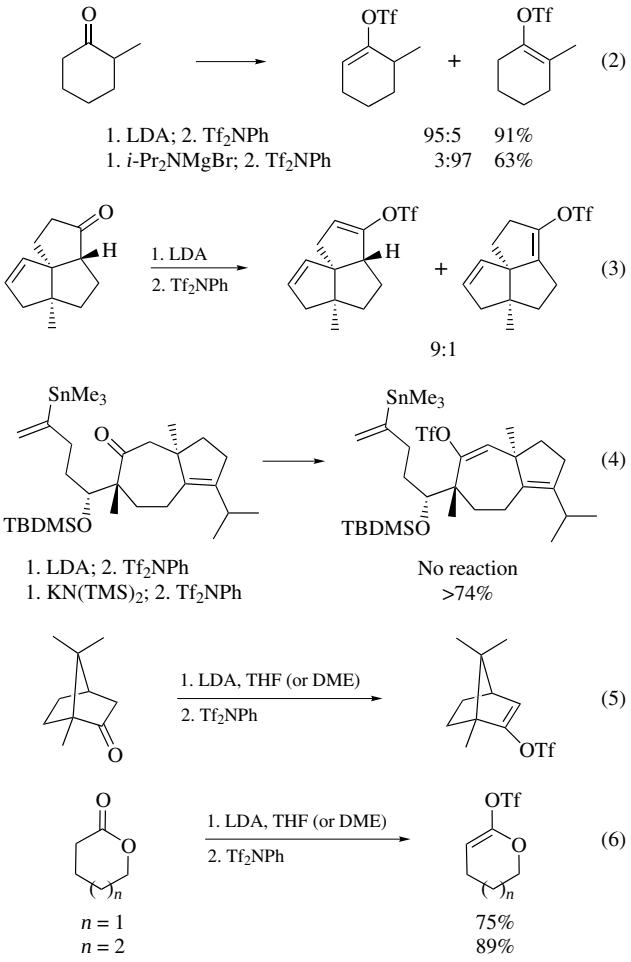
Utility and Selectivity with Amines and Alcohols. The trifluoromethanesulfonyl group provides for effective protection of primary and secondary amines[4] and the monoalkylation of secondary trifluoromethanesulfonamides.[3] These substrates are typically formed by the reaction of the amine with trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O). As a less reactive triflating reagent, *N*-phenyltrifluoromethanesulfonimide[2] (Tf_2NPh) is more convenient to use and provides higher selectivity than that encountered with triflic anydride. Triflates of secondary aliphatic amines are easily isolated from the byproduct phenyltriflamide by carbonate extraction[3] and Tf_2NPh does not react with aromatic secondary amines under similar or more vigorous conditions.[3] This selectivity is also observed in selective triflation of primary over secondary alcohols, allowing selective dehydration in a series of dipeptides (eq 1).[9]



(1)

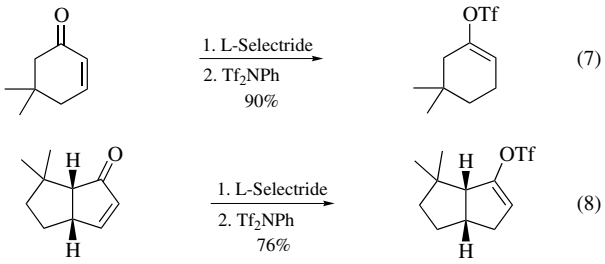
R^1 = Me, R^2 = CH_2Ph	70%
R^1 = Me, R^2 = *t*-Bu	71%
R^1 = Ph, R^2 = CH_2Ph	81%

Formation of Enol Trifluoromethanesulfonates (Enol Triflates). Kinetic or thermodynamic enolate formation, through reaction of unsymmetrical ketones with properly selected strong bases, followed by treatment with Tf_2NPh provides regioselective formation of vinyl triflates[7,8,10,11] in good to excellent yields (eq 2). Minor discrepancies to these generalities have been documented, but appear to be substrate (eq 3)[12,13] or base dependent (eq 4).[13] This sequence surpasses the triflic anhydride/base protocol (which provides predominantly thermodynamic products) both in regiocontrol and material yield and has led to preparation of enol triflates where triflic anhydride fails (eq 5).[7,14–16] Enol triflates of symmetrical and unidirectionally enolizable ketones[13,14,17–20] are produced in typically higher yield by trapping with Tf_2NPh compared with Tf_2O[7,16] or (trifluoromethylsulfonyl)imidazole[14,17] and enolates of five- to seven-membered lactones have been isolated as their trifluoromethanesulfonyl ketene acetals (eq 6).[21]



Regiospecific Generation of Enol Triflates. A variety of enolate generation methods followed by exposure to Tf_2NPh provides regiospecific vinyl triflates. Regiospecific enolates generated from conjugate reduction of enones with lithium[7,22] in liquid ammonia, from pure silyl enol ethers with methyllithium,[6] and by conjugate addition of dialkylcuprate reagents to enones[6,23] are all successfully trapped by Tf_2NPh. *N*-Phenyltriflimide efficiently captures regiospecific enolates generated from conjugate reduction of cyclopentenones[6] and cyclohexenones[6,24] with lithium *Tri-sec*-butylborohydride (eqs 7 and 8), with the exception of sterically encumbered substrates.[6] *N*-Phenyltriflimide has become a widely utilized reagent for the conversion of phenols to aryl triflates. Optimal yields[2] and chemoselectivity[2,25] allow aryl triflate

formation in the presence of amines, alcohols, or carboxylates[2] and on relatively sensitive substrates.[25]



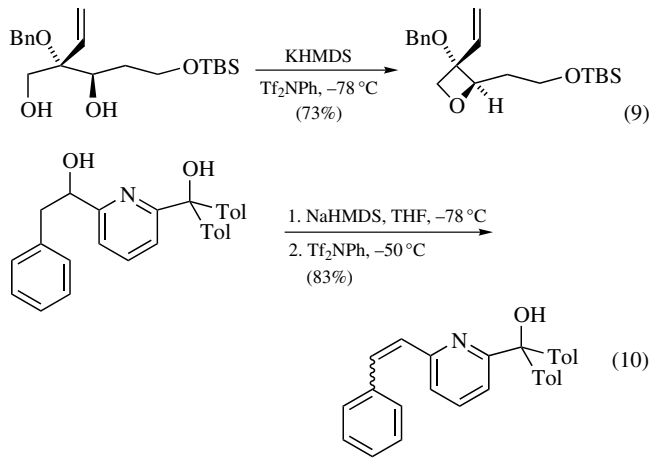
Utility of Enol and Aryl Triflates. Enol triflates have been utilized for the generation of vinyl cations and carbenes,[26] and the transient 1,2,3-cyclohexatriene.[27] Enol triflates and trifluoromethanesulfonyl ketene acetals[21] undergo coupling with diorganocuprate reagents to give alkenes and substituted enol ethers, respectively. Palladium-catalyzed coupling and carbonylation reactions of enol and aryl triflates with organostannanes, alkenes, and alkynes abound in the literature.[14]

Other Applications. A selected number of primary and secondary saturated triflones are available from the reaction of the respective alkyllithium or dialkylcuprate reagent with *N*-phenyltriflimide.[28]

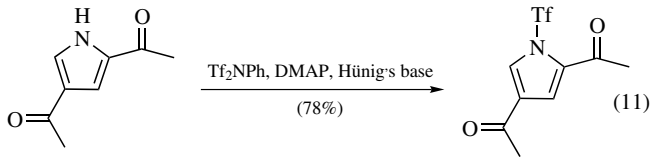
First Update

Ralf Schwörer
Industrial Research Limited, Lower Hutt, New Zealand

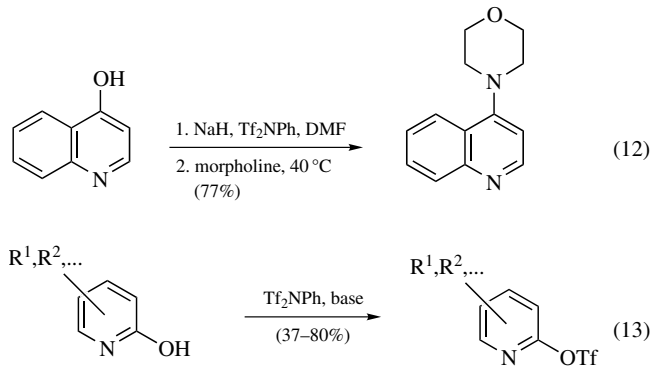
Utility and Selectivity with Amines and Alcohols. *N*-Phenyltrifluoromethanesulfonimide (Tf_2NPh) is widely used to triflate alcohols and amines. As a milder triflating agent compared to triflic anhydride (Tf_2O), it proves to be useful for the selective formation of triflates. A primary alcohol was transformed into its triflate in the presence of a secondary alcohol and subsequently reacted to form an oxetane of the desired stereochemistry (eq 9).[29] Triflation of a secondary over a tertiary alcohol allows dehydration to form a conjugated olefin (eq 10).[30] Tf_2O induced partial decomposition in this case.[30]



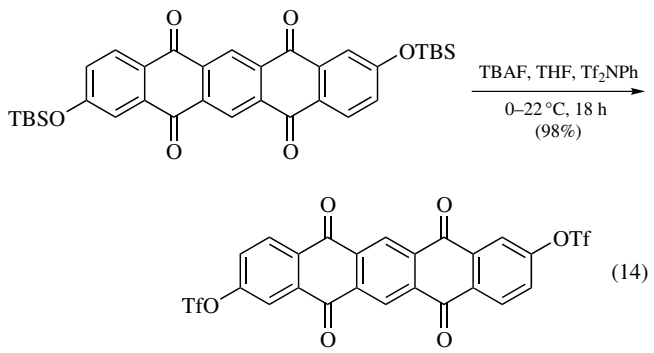
N-Triflation of a substituted pyrrole was achieved by reacting 2,4-diacetylpyrrole with Tf_2NPh, Hünig's base, and DMAP (eq 11).[31]



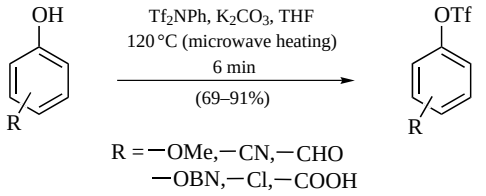
Formation of Aryl and Heteroaryl Triflates. Nitrogen-containing heterocycles bearing amino substituents are often of interest for pharmaceutical applications. 4- and 2-hydroxyquinolines have been converted to their triflates with Tf_2NPh and reacted with primary and secondary aliphatic and aromatic amines to afford the corresponding amines in good yields.[32] As an example, a morpholino derivative was synthesized by a one-pot procedure in 77% yield over two steps (eq 12).[32] A number of substituted hydroxy pyridines have been reacted with Tf_2NPh using NaH or triethylamine as base to afford the corresponding heteroaryl triflates (eq 13).[33–35]



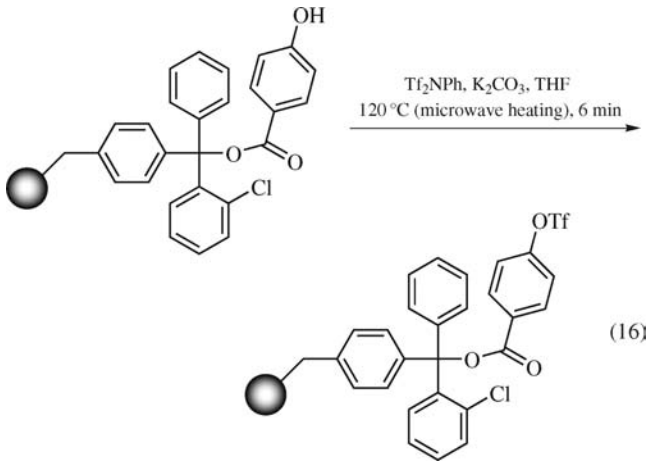
Aryl silyl ethers were directly converted to aryl triflates by desilylation with TBAF/THF and direct addition of Tf_2NPh to the TBAF/THF reaction mixture (eq 14).[36]



The reaction times for the synthesis of aryl triflates from phenols have been reduced from several hours to 6 min by means of controlled microwave heating. The methodology was applied to a number of substrates (eq 15) under solution- and solid-phase (one example) conditions (eq 16).[37]

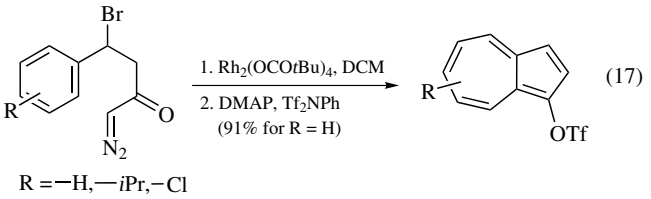


(15)



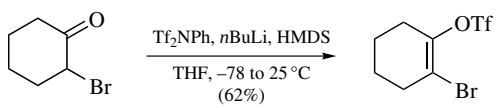
(16)

Tf_2NPh was successfully employed in the synthesis of substituted azulenes.[38,39] Unstable 1-hydroxyazulenes were formed by a "ring expansion–annulation" strategy and trapped in situ by Tf_2NPh as triflate esters (eq 17), which were utilized in Suzuki coupling reactions.

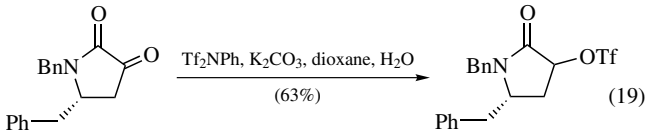


(17)

Formation of Enol Trifluoromethanesulfonates (Enol Triflates). Enol triflates can be formed by generating enolates with an appropriate strong base and trapping the enolate with a triflating agent. Tf_2NPh is often used where other triflating methods fail.[7,14–16] Tf_2NPh consistently gave the best yields in the synthesis of a bromo hexenyltriflate (eq 18)[40] compared to other methods.[41] The use of Tf_2NPh facilitated the scale-up of the reaction to 30 mmol, while the isolated yields dropped considerably when using Tf_2O on a scale of more than 1 mmol.[40] A demanding substrate with a potentially labile stereocenter was converted to an enol triflate without observing any racemization (eq 19).[42] Other triflating agents such as Tf_2O and *N*-pyridyltrifluoromethanesulfonimides[43] were significantly less effective in this reaction.[42]

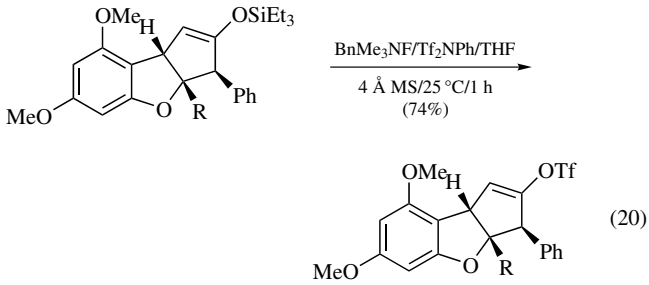


(18)

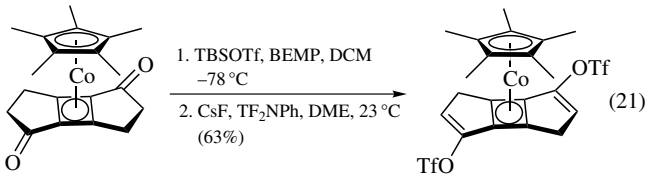


(19)

New methods have been developed for the conversion of silyl enol ethers to vinyl triflates as an alternative to the use of methyllithium.[6] A source of fluoride (CsF[44] or $BnMe_3NF$[45]) is used in combination with Tf_2NPh to cleave the silyl ether and trap the generated enolates as their triflates. CF_3SO_2F is generated in situ and appropriate measures have to be taken to prevent the escape of this gaseous reagent.[44] Tf_2NPh is necessary for the reaction to proceed, as CF_3SO_2F alone or mixtures of CF_3SO_2F/CsF fail to promote the desired transformation.[44] This methodology was successfully applied in the synthesis of vinyl triflates in five- and six-membered rings as well as open-chain derivatives from their corresponding TMS[46], TES[45] (eq 20), or TBS[44] enol ethers or starting from a ketone[47] (eq 21).

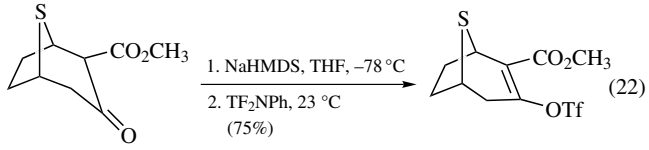


(20)

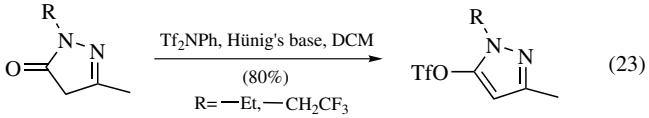


(21)

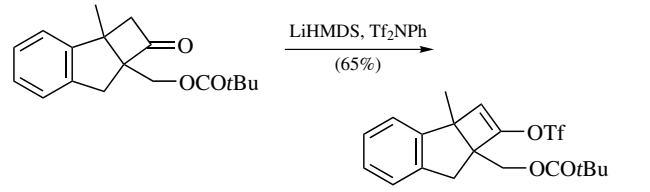
Tf_2NPh has been widely used on a variety of substrates to provide enol triflates, mostly regiospecifically, demonstrating the scope and utility of this reagent.[41] Tf_2NPh was further employed to generate enol triflates of heterocycles, starting from thiabicyclooctanones[48] (eq 22) or pyrazolones[49] (eq 23) as examples. Enolates of 4-[50] and up to 8-[51,52] and 12-membered[51] cyclic ketones (eqs 24 and 25) were successfully captured by Tf_2NPh, as well as enolates derived from diketones[53,54] (eq 26) and β-keto lactams[55] (eq 27).



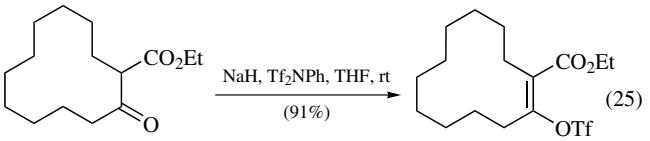
(22)



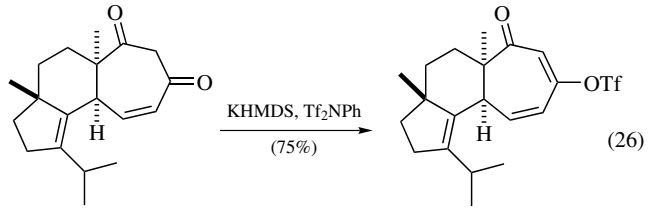
(23)



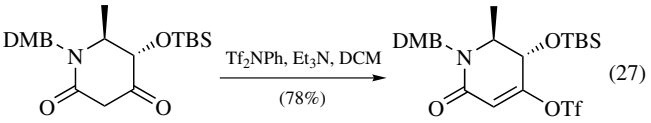
(24)



(25)

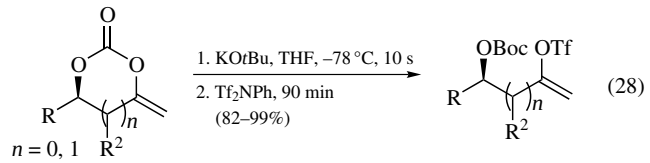


(26)



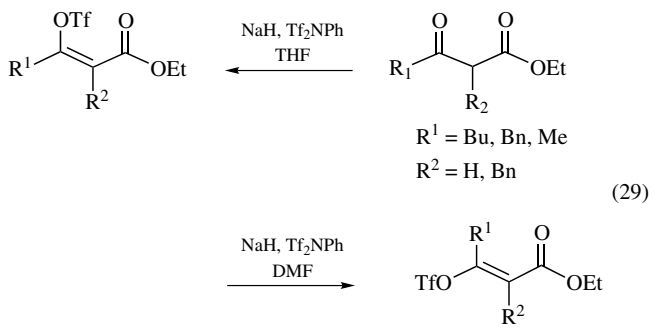
(27)

Cyclic enol carbonates have been converted to enol triflates in excellent yields using Tf_2NPh (eq 28).[56]

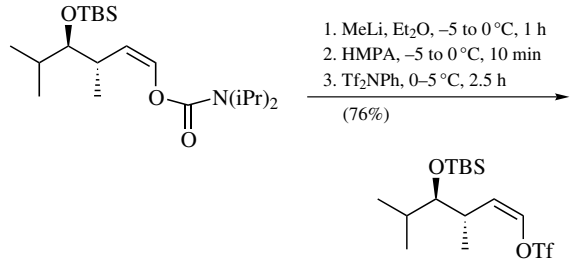


(28)

Stereoselective Formation of (*E*/*Z*)-Enol Triflates. The stereoselective formation of vinyl triflates can be achieved by choice of the right solvent.[41] Depending on the solvent used for the reaction of β-keto esters, either the (*E*)- or (*Z*)-triflates are obtained (eq 29).[57,58] Using diethyl ether as solvent and DMPU or HMPA as additive together with Tf_2NPh helps to capture a (*Z*)-triflate in good yields (eq 30).[59] In another example, the stereochemical outcome is dependent on the water content of the reaction mixture.[60] The stereoselective synthesis of an (*E*)-enol triflate using KO*t*Bu, 18-crown-6, and Tf_2NPh was achieved by addition of 0.5 equiv of water to the reaction (eq 31); under anhydrous conditions, the stereoselectivity and yield were poorer.[60]



(29)



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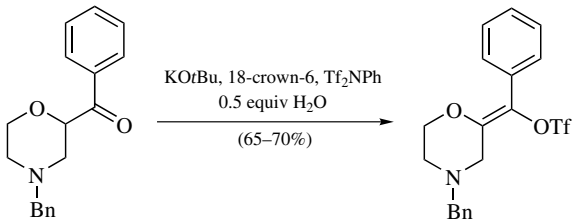


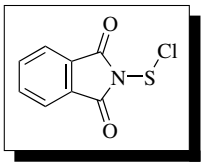
(31)

Utility of Enol and Aryl Triflates. Enol and aryl triflates are extensively used for cross-coupling reactions, the formation of carbon–carbon, carbon–tin, carbon–nitrogen, carbon–sulfur, carbon–phosphorus, and carbon–halogen bonds, and reduction/deoxygenation.[41] In recent examples, they were used to form enamines[61] or enamides[62] or were eliminated to cyclooctynes[63] for copper-free cycloadditions in biological systems.

1. *Fieser & Fieser* **1986**, *12*, 395; **1988**, *13*, 248.
2. Hendrickson, J. B.; Bergeron, R., *Tetrahedron Lett.* **1973**, 4607.
3. Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D., *Tetrahedron* **1975**, *31*, 2517.
4. Greene, T. W.; Wuts, P. G. M., *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.
5. Scott, W. J.; Crisp, G. T.; Stille, J. K., *J. Am. Chem. Soc.* **1984**, *106*, 4630.
6. Crisp, G. T.; Scott, W. J., *Synthesis* **1985**, 335.
7. McMurry, J. E.; Scott, W. J., *Tetrahedron Lett.* **1983**, *24*, 979.
8. Corey, E. J.; Wu, L. I., *J. Am. Chem. Soc.* **1993**, *115*, 9327.
9. Torrini, I.; Zecchini, G. P.; Paradisi, M. P., *Synth. Commun.* **1989**, *19*, 695.
10. Crisp, G. T.; Scott, W. J.; Stille, J. K., *J. Am. Chem. Soc.* **1984**, *106*, 7500.
11. Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A., *Tetrahedron* **1991**, *47*, 3485.
12. Cheney, D. L.; Paquette, L. A., *J. Org. Chem.* **1989**, *54*, 3334.
13. Piers, E.; Friesen, R. W., *Can. J. Chem.* **1992**, *70*, 1204.
14. Scott, W. J.; McMurry, J. E., *Acc. Chem. Res.* **1988**, *21*, 47.
15. Paquette, L. A.; Moriarty, K. J.; McKinney, J. A.; Rogers, R. D., *Organometallics* **1989**, *8*, 1707.
16. Nakatani, K.; Arai, K.; Hirayama, N.; Matsuda, F.; Terashima, S., *Tetrahedron* **1992**, *48*, 633.
17. Subramanian, L. R.; Bentz, H.; Hanack, M., *Synthesis* **1973**, 293.
18. Thompson, S. K.; Heathcock, C. H., *J. Org. Chem.* **1990**, *55*, 3004.
19. Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J., *J. Org. Chem.* **1992**, *57*, 4043.
20. Freskos, J. N.; Ripin, D. H.; Reilly, M. L., *Tetrahedron Lett.* **1993**, *34*, 255.
21. Tsushima, K.; Araki, K.; Murai, A., *Chem. Lett.* **1989**, 1313.
22. Holt, D. A.; Levy, M. A.; Oh, H.-J.; Erb, J. M.; Heaslip, J. I.; Brandt, M.; Lan-Hargest, H.-Y.; Metcalf, B. W., *J. Med. Chem.* **1990**, *33*, 943.

23. Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K., *J. Org. Chem.* **1986**, *51*, 277.
24. Scott, W. J.; Peña, M. R.; Swärd, K.; Stoessel, S. J.; Stille, J. K., *J. Org. Chem.* **1985**, *50*, 2302.
25. Petrakis, K. S.; Nagabhushan, T. L., *J. Am. Chem. Soc.* **1987**, *109*, 2831.
26. (a) Stang, P. J., *Acc. Chem. Res.* **1978**, *11*, 107. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R., *Synthesis* **1982**, 85.
27. Shakespeare, W. C.; Johnson, R. P., *J. Am. Chem. Soc.* **1990**, *112*, 8578.
28. Hendrickson, J. B.; Bair, K. W., *J. Org. Chem.* **1977**, *42*, 3875.
29. Paquette, L. A.; Shin, T.-L.; Zeng, Q.; Hofferberth, J. E., *Tetrahedron Lett.* **1999**, *40*, 3519.
30. Moitessier, N.; Chapleur, Y., *Tetrahedron Lett.* **2003**, *44*, 1731.
31. Chrétien, A.; Chataigner, I.; Piettre, S. R., *Tetrahedron* **2005**, *61*, 7907.
32. Cacchi, S.; Carangio, A.; Fabrizi, G.; Moro, L.; Pace, P., *Synlett* **1997**, 1400.
33. Torrado, A.; Imperiali, B., *J. Org. Chem.* **1996**, *61*, 8940.
34. Zhao, H.; Serby, M. D.; Xin, Z.; Szczepankiewicz, B. G.; Liu, M.; Kosogof, C.; Liu, B.; Nelson, L. T. J.; Johnson, E. F.; Wang, S.; Pederson, T.; Gum, R. J.; Clampit, J. E.; Haasch, D. L.; Abad-Zapatero, C.; Fry, E. H.; Rondinone, C.; Trevillyan, J. M.; Sham, H. L.; Liu, G., *J. Med. Chem.* **2006**, *49*, 4455.
35. Hunt, J. C. A.; Briggs, E.; Clarke, E. D.; Whittingham, W. G., *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5222.
36. Bénard, C. P.; Geng, Z.; Heuft, M. A.; VanCrey, K.; Fallis, A. G., *J. Org. Chem.* **2007**, *72*, 7229.
37. Bengtson, A.; Hallberg, A.; Larhed, M., *Org. Lett.* **2002**, *4*, 1231.
38. Kane, J. L.; Shea, K. M.; Crombie, A. L.; Danheiser, R. L., *Org. Lett.* **2001**, *3*, 1081.
39. Crombie, A. L.; Kane, J. L.; Shea, K. M.; Danheiser, R. L., *J. Org. Chem.* **2004**, *69*, 8652.
40. von Zezschwitz, P.; Petry, F.; de Meijere, A., *Chem. Eur. J.* **2001**, *7*, 4035.
41. Ritter, K., *Synthesis* **1993**, 735.
42. Bower, J. F.; Williams, A. J.; Woodward, H. L.; Szeto, P.; Lawrence, R. M.; Gallagher, T., *Org. Biomol. Chem.* **2007**, *5*, 2636.
43. Comins, D. L.; Dehghani, A., *Tetrahedron Lett.* **1992**, *33*, 6299.
44. Mi, Y.; Schreiber, J. V.; Corey, E. J., *J. Am. Chem. Soc.* **2002**, *124*, 11290.
45. Magnus, P.; Stent, M. A. H., *Org. Lett.* **2005**, *7*, 3853.
46. Hong, S.; Corey, E. J., *J. Am. Chem. Soc.* **2006**, *128*, 1346.
47. Myers, A. G.; Sogi, M.; Lewis, M. A.; Arvedson, S. P., *J. Org. Chem.* **2004**, *69*, 2516.
48. Meltzer, P. C.; Pham-Huu, D.-P.; Madras, B. K., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6007.
49. Dirat, O.; Clipson, A.; Elliott, J. M.; Garrett, S.; Jones, A. B.; Reader, M.; Shaw, D., *Tetrahedron Lett.* **2006**, *47*, 1729.
50. Bonnaud, B.; Mariet, N.; Vacher, B., *Eur. J. Chem.* **2006**, 246.
51. Watanabe, N.; Tanino, K.; Kuwajima, I., *Tetrahedron Lett.* **1999**, *40*, 8133.
52. Wada, A.; Tsutsumi, M.; Inatomi, Y.; Imai, H.; Shichida, Y.; Ito, M., *J. Chem. Soc., Perkin Trans. 1* **2001**, 2430.
53. Snider, B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M., *J. Am. Chem. Soc.* **1996**, *118*, 7644.
54. Hughes, C. C.; Trauner, D., *Angew. Chem., Int. Ed.* **2002**, *41*, 1569.
55. Sasaki, Y.; Niida, A.; Tsuji, T.; Shigenaga, A.; Fujii, N.; Otaka, A., *J. Org. Chem.* **2006**, *71*, 4969.
56. Maddess, M. L.; Lautens, M., *Synthesis* **2004**, 1399.
57. Keenan, R. M.; Weinstock, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Hill, D. T.; Morgan, T. M.; Samanen, J. M.; Hempel, J.; Eggleston, D. S.; Aiyar, N.; Griffin, E.; Ohlstein, E. H.; Stack, E. J.; Weidley, E. F.; Edwards, R., *J. Med. Chem.* **1992**, *35*, 3858.
58. Crisp, G. T.; Meyer, A. G., *J. Org. Chem.* **1992**, *57*, 6972.
59. Porée, F.-H.; Barbion, J.; Dhulut, S.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J., *Synthesis* **2004**, 3017.
60. Agejas, J.; Lamas, C., *Tetrahedron Lett.* **2007**, *48*, 2603.
61. Willis, M. C.; Brace, G. N., *Tetrahedron Lett.* **2002**, *43*, 9085.
62. Wallace, D. J.; Klauber, D. J.; Chen, C.; Volante, R. P., *Org. Lett.* **2003**, *5*, 4749.
63. Agard, N. J.; Baskin, J. M.; Prescher, J. A.; Lo, A.; Bertozzi, C. R., *ACS Chem. Biol.* **2006**, *1*, 644.

Phthalimidosulfenyl Chloride[1]



[54974-07-1] $C_8H_4ClNO_2S$ (MW 213.65)

InChI = 1/C8H4ClNO2S/c9-13-10-7(11)5-3-1-2-4-6(5)8(10)12/h1-4H

InChIKey = AQKMFIZDSMHXQR-UHFFFAOYAV

(reacts as a pseudohalogen;[1] synthetic equivalent of inaccessible sulfenyl chlorides;[2,3,5] adds across double and triple bonds;[2–5] reagent for the formation of episulfides;[6] reacts with ketones to give β-keto sulfides[7])

Alternative Names: phthalimide-*N*-sulfenyl chloride; 1,3-dihydro-1,3-dioxo-2*H*-isoindole-2-sulfenyl chloride; *N*-(chlorothio)phthalimide.

Physical Data: mp 115–117 °C.

Solubility: sol chlorobenzene, benzene, CH_2Cl_2, MeOH; insol pentane.

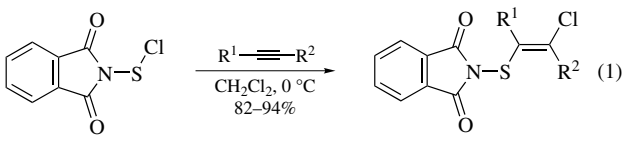
Form Supplied in: yellow crystals; not commercially available.

Preparative Method: prepared by treatment of potassium phthalimide with S_2Cl_2 to form the disulfide which is then cleaved with chlorine in warm chloroform.[1]

Purification: recrystallization from methanol.

Handling, Storage, and Precautions: can be stored at 0 °C for several months.

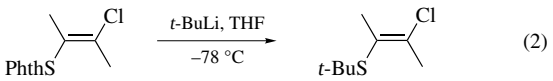
Addition to Alkynes. Phthalimidosulfenyl chloride adds to unsymmetrically substituted alkynes, via a thiirenium ion, to give regioisomeric mixtures of (*E*)-β-chlorovinyl sulfenamides arising predominantly from anti-Markovnikov addition (eq 1).[2,3]



(1)

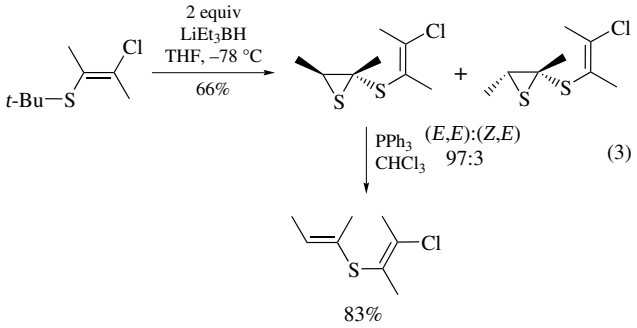
Alkynes	Adducts anti-M:M
R^1 = Bu, R^2 = H	89:11
R^1 = *t*-Bu, R^2 = H	100:0
R^1 = Ph, R^2 = H	85:15
R^1 = Me, R^2 = Ph	100:0

The sulfur–nitrogen bond of the alkyne adduct enhances this reagent's usefulness since the sulfenamide products are mild sulfur electrophiles, useful for the introduction of sulfur-substituted residues into organic molecules. The phthalimido group has been displaced with various nucleophiles such as carbanions,[2–4,8,9] amines,[2–4,10] thiols,[11] and alcohols;[12] the regio- and stereochemical integrity of the double bond is maintained during such displacements. This suggests that phthalimidosulfenyl chloride may be considered a synthetic equivalent of synthetically inaccessible sulfenyl chlorides such as *t*-butylsulfenyl chloride and *N*,*N*-bis(trimethylsilyl)aminosulfenyl chloride (eq 2).[2–4]



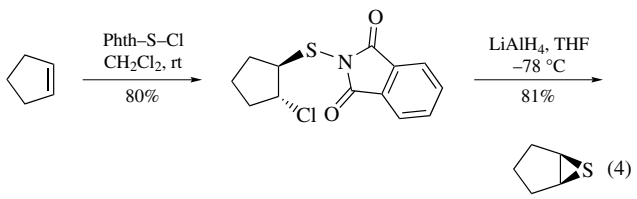
(2)

Reaction of the alkyne adducts with aluminum and boron hydride reagents such as lithium aluminum hydride, sodium borohydride, or lithium triethylborohydride, however, leads to the formation of unexpected thiirane derivatives (eq 3).[13] These can be desulfurized to give divinyl sulfides.



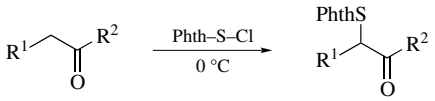
(3)

Addition to Alkenes. Phthalimidosulfenyl chloride can be added to alkenes to yield α-chloro thioethers[5] which, after treatment with lithium aluminum hydride, produce episulfides (eq 4).[6] Sodium borohydride is unsuccessful in transforming the alkene adduct to the episulfide. The alkene addition is stereospecifically *trans* and proceeds through a thiiranium ion intermediate, the opening of which is governed predominantly by steric factors and usually gives a predominance of the anti-Markovnikov addition product.[14] As in the addition of phthalimidosulfenyl chloride to alkynes, the phthalimido group can also be displaced with nucleophiles.[4]



(4)

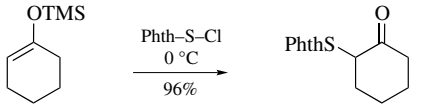
Reaction with Enolizable Carbonyl Compounds. Good yields of β-keto thioadducts can be obtained from the reaction of phthalimidosulfenyl chloride with ketones at 0 °C using the required carbonyl compound as solvent (eq 5).[5,7] β-Diketones and β-keto esters also react in this manner.[7]



(5)

R^1	R^2	% yield
H	Me	85
H	Ph	71
Me	Ph	87

In contrast, cyclohexanone does not react under the above conditions. The corresponding adduct can be formed by reaction of the trimethylsilyl enol ether with phthalimidosulfenyl chloride (eq 6).[7]



(6)

1. (a) Capozzi, G.; Modena, G.; Pasquato, L. In *The Chemistry of Sulphenic Acids and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1990; p 403. (b) Kuehle, E. *The Chemistry of Sulphenic Acids*; Theime: Stuttgart, 1973.
2. Capozzi, G.; Gori, L.; Menichetti, S., *Tetrahedron Lett.* **1990**, *31*, 6213.
3. Capozzi, G.; Gori, L.; Menichetti, S., *Phosphorus Sulfur/Phosphorus Sulfur Silicon* **1991**, *59*, 157.
4. Capozzi, G.; Gori, L.; Menichetti, S.; Nativi, C., *J. Chem. Soc., Perkin Trans. 1* **1992**, 1923.
5. Mullin, V. A.; Zolotov, A. N., *J. Gen. Chem. USSR (Engl. Transl.)* **1986**, *56*, 791.
6. Bombala, M. U.; Ley, S. V., *J. Chem. Soc., Perkin Trans. 1* **1979**, 3013.
7. Capozzi, G.; Menichetti, S.; Nativi, C.; Rosi, A., *Tetrahedron* **1992**, *41*, 9023.
8. Busi, E.; Capozzi, G.; Menichetti, S.; Nativi, C., *Synthesis* **1992**, 643.
9. Grossert, S. J.; Dubey, P. K., *J. Chem. Soc., Chem. Commun.* **1982**, 1183.
10. Harpp, D. N.; Back, G. T., *Tetrahedron Lett.* **1971**, 4953.
11. (a) Harpp, D. N.; Ash, D. K.; Back, G. T.; Gleason, G. J.; Orwig, A. B.; VanHorn, W. F., *Tetrahedron Lett.* **1970**, 3551. (b) Boustany, K. S.; Sullivan, A. B., *Tetrahedron Lett.* **1970**, 3547. (c) Harpp, D. N.; Back, T. G., *J. Org. Chem.* **1971**, *36*, 3828.
12. Barton, D. H. R.; Page, G.; Widdowson, D. A., *J. Chem. Soc., Chem. Commun.* **1970**, 1466.
13. Capozzi, G.; Gori, L.; Menichetti, S., *Tetrahedron* **1991**, *47*, 7185.
14. Mueller, W. H., *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 482.

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Potassium *tert*-Butoxide–Dimethyl Sulfoxide[1]

t-BuOK/Me_2SO

(*t*-BuOK)
[865-47-4] C_4H_9KO (MW 112.23)
InChI = 1/C4H9O.K/c1-4(2,3)5;/h1-3H3;/q-1;+1
InChIKey = LPNYRYFBWFDTMA-UHFFFAOYAU
(DMSO)
[67-68-5] C_2H_6OS (MW 78.15)
InChI = 1/C2H6OS/c1-4(2)3/h1-2H3
InChIKey = IAZDPXIOMUYVGZ-UHFFFAOYAR

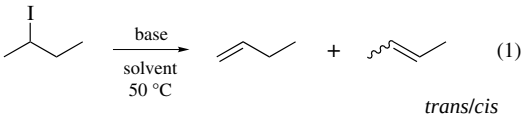
(highly basic reagent; useful for β-elimination and alkene isomerization reactions[1])

Preparative Methods: prepared in situ from anhydrous *t*-BuOK and anhydrous DMSO.[2a] Anhydrous DMSO is prepared by distillation from calcium hydride or sodium hydride under reduced pressure at 60 °C.

Handling, Storage, and Precautions: see Potassium *tert*-butoxide and dimethyl sulfoxide. Store over 4 molecular sieves.[2b] Use in a fume hood.

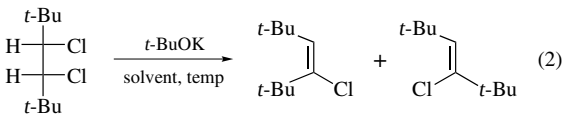
Introduction. Solutions of *t*-BuOK in DMSO are highly basic because the solvent strongly complexes with potassium cations, producing activated ligand-separated and dissociated *t*-butoxide anions in a medium of high dielectric constant.[1,2a,3] This base/solvent system is capable of deprotonating weakly acidic carbon and other acids.[2a,3] It is widely used to effect β-elimination reactions and isomerizations of unsaturated systems.[1,2a,3] $DMSO^-K^+$ is present in low concentrations in *t*-BuOK/DMSO solutions.[4]

β-Elimination Reactions. A change in solvent from *t*-BuOH to DMSO affects the regiochemistry and stereochemistry of β-eliminations of alkyl halides with *t*-BuOK. For example, for 2-iodobutane both the 2-butene:1-butene and the *trans*:*cis*-2-butene ratios are increased (eq 1).[6] This is because the base is much more hindered in *t*-BuOH, where it is highly aggregated, than in DMSO, where the equilibrium is shifted toward less bulky free *t*-butoxide anions.[1–6] Chlorocyclodecane is dehydrochlorinated to *cis*-cyclodecene in good yield with *t*-BuOK/DMSO.[7a] Interestingly, if the elimination is effected with lithium dicyclohexylamide in Et_2O–hexane, the *trans*-isomer is produced. It was suggested that the dissociated *t*-butoxide anion should favor *anti* elimination, while the associated amide base should favor *syn* elimination.[1] However, it was later shown that isomerization of the thermodynamically less stable *trans*-isomer to the more stable *cis*-isomer accounts for the formation of the latter with *t*-BuOK/DMSO.[7b] For hindered acyclic substrates the reagent favors the usual *anti*-coplanar β-elimination mechanism, whereas *syn* elimination is the major pathway when solutions of the base in THF or *t*-BuOH are employed (eq 2).[3] Presumably, the aggregated ion pairs of the base in the latter solvents assist in the removal of the leaving group and the β-proton in a *syn* alignment.[5,8] *Anti* elimination also results when 18-Crown-6 is added to THF solutions of *t*-BuOK because dissociated *t*-butoxide anions are produced. The strained alkene 3,3-dimethylcyclopropene is obtained in good yield from 1-halo-2,2-dimethylcyclopropanes with the reagent;[9] the presence of *t*-BuOH reduces the yield considerably.



(1)

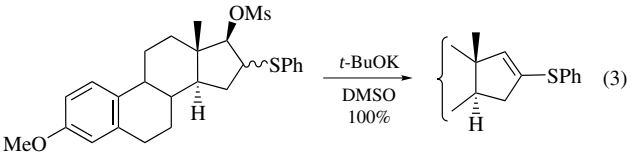
Base/solvent			*trans*/*cis* 2-butene ratio
t-BuOK/DMSO	~21%	~79%	2.99
t-BuOK/*t*-BuOH	34%	66%	2.17



(2)

Solvent/temp		
DMSO, 20 °C	93	7
THF, 60 °C	8	92
THF + 18-crown-6, 60 °C	87	13

β-Phenylthio chlorides, tosylates, and mesylates undergo β-elimination to vinyl sulfides in high yield upon treatment with *t*-BuOK/DMSO (eq 3).[10] This type of reaction is an important step in a synthetically useful 1,2-carbonyl transposition sequence.[10]

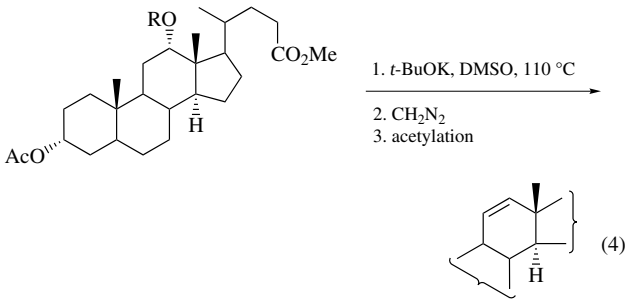


(3)

Primary tosylates are more prone than bromides to form *t*-butyl ethers by S_N2 displacement by the *t*-butoxide anion in DMSO.[11] Sulfonate esters of flexible cyclic and secondary acyclic alcohols give predominately alkenes in the presence of *t*-BuOK/DMSO.[12] With sulfonate esters of 3-hydroxy steroids, there is competition between β-elimination and attack of the *t*-butoxide ion on sulfur to form alcohols;[13] mesylates are more prone to this reaction than tosylates. Sulfonate esters of 3α-acetoxy-12α-hydroxycholanate undergo mainly β-elimination with *t*-BuOK/DMSO (eq 4).[14] In this case, substitution of various other aprotic solvents for DMSO and $DMSO^-Na^+$ for *t*-BuOK was not as effective. Treatment of both the mesylate and the tosylate of cholesterol with *t*-BuOK/DMSO gives the conjugated diene, 3,5-cholestadiene, in high yield.[15]

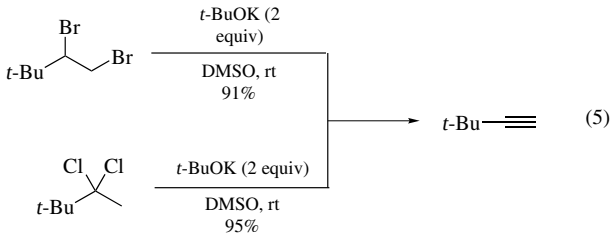
1,2-Dibromo-[16a] and 2,2-dichloro-3,3-dimethylbutane derivatives[16b] undergo double dehydrohalogenation with *t*-BuOK/DMSO to yield *t*-butylacetylene (eq 5). The reagent converts eight- and nine-membered ring 2-bromo-3-methoxy *trans*-cycloalkenes into the corresponding methoxy cycloalkynes via *anti* elimination in reasonably good yields (eq 6).[17] 1-Chloro-4-methylcyclohexene is converted largely into the corresponding 1-*t*-butyl ether derivative in the presence of the base (eq 7).[18] An allene, 5-methyl-1,2-cyclohexadiene, is probably an intermediate in the reaction. The related allene derived from 1-bromocyclohexene

has been trapped with 1,3-diphenylbenzo[*c*]furan under similar conditions.[19] *t*-BuOK/DMSO reacts with bromobenzene to give *t*-butyl phenyl ether in low yield, presumably via the intermediacy of benzyne.[20]

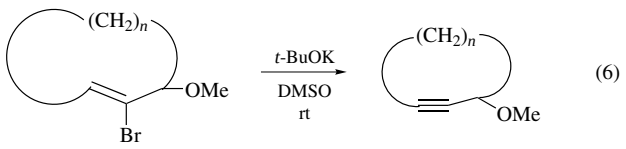


(4)

R = Ts, ~74%; Ms, ~55%

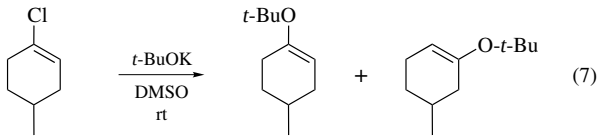


(5)



(6)

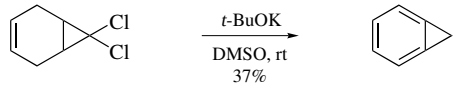
n = 5, 74%
n = 6, 70%



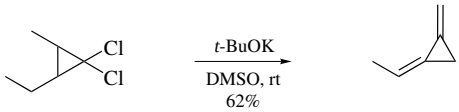
(7)

98% 2%

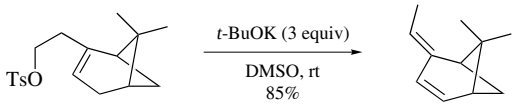
***β*-Elimination with Double Bond Isomerization.** *t*-BuOK in DMSO is sufficiently basic to isomerize less thermodynamically stable multiple bond systems to more stable isomeric compounds (see below). Therefore, it is not surprising that *β*-eliminations with this reagent are frequently accompanied by isomerizations of initially formed products. *gem*-Dihalocyclopropane derivatives are particularly prone to these reactions (eqs 8 and 9);[21] such reactions may also occur with *t*-BuOK in other solvents.[21c] Certain *gem*-dichlorocyclopropanes yield enynes by processes involving cleavage of the three-membered ring upon reaction with *t*-BuOK/DMSO.[21d,e] The base converts 7,7-dichlorobicyclo-[4.1.0]heptane to a complex mixture of products containing mainly ethylbenzene.[22] The extra carbon atom apparently comes from the solvent, DMSO. An example of an isomerization of an initially formed diene to a more stable isomer is found in the reaction of the tosylate of the terpene alcohol nopol with excess *t*-BuOK/DMSO (eq 10).[23]



(8)

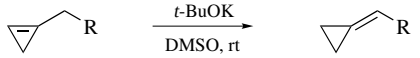


(9)



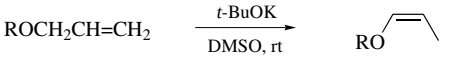
(10)

Isomerizations of Unsaturated Systems. *t*-BuOK/DMSO is a sufficiently powerful base to produce carbanions in a low equilibrium concentration by the deprotonation of sp^3-hybridized carbon atoms adjacent to multiple C–C bonds.[1] Thus the base can effect isomerizations of less thermodynamically stable unsaturated systems to more stable isomers. The rearrangement of terminal alkenes into internal isomers,[2a,3] alkylcyclopropenes into alkylidenecyclopropanes (eq 11),[24] and a variety of allylic compounds into the corresponding vinylic compounds are representative examples of these reactions. It is interesting that this base converts allyl ethers to *cis*-enol ethers stereospecifically and in high yields (eq 12).[25]



(11)

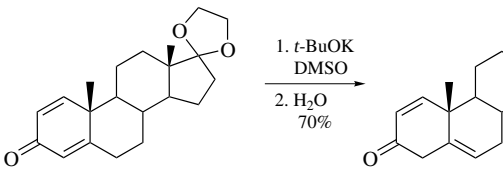
R = H, 100%
R = Me, 85%



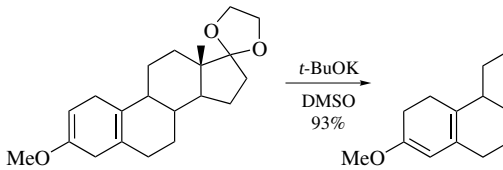
(12)

R = Ph, 99%
R = O, 85–90%

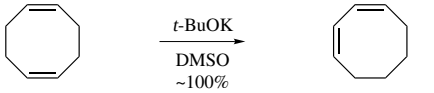
The base converts steroidal 1,4-dien-3-ones into 1,3,5-trienolates which yield 1,5-dien-3-ones upon addition of water (eq 13).[26] This reaction does not occur with *t*-BuOK/*t*-BuOH. The *t*-BuOK/DMSO reagent isomerizes cyclic 1,4- (eq 14)[27] and 1,5-dienes (eq 15)[28] into the corresponding conjugated dienes.



(13)

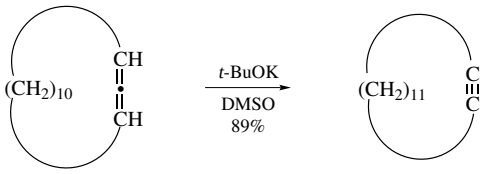


(14)



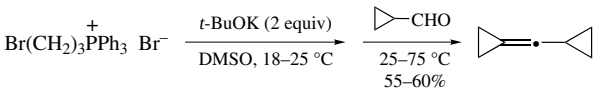
(15)

Acyclic enynes and cumulenes are converted into conjugated trienes with a catalytic amount of *t*-BuOK in DMSO.[29] The conversion of a cyclic allene into a cyclic alkyne (eq 16) occurs with this base, while potassium *tert*-butoxide–*tert*-butyl alcohol complex.



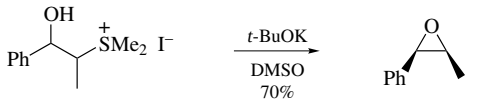
(16)

Other Reactions. In the reaction shown in eq 17, *t*-BuOK/DMSO effects the conversion of a γ-bromophosphonium salt into a cyclopropylidenephosphorane which reacts with cyclopropanecarbaldehyde to form cyclopropylmethylenecyclopropane.[31] This product is converted into dicyclopropylidenemethane in two steps.

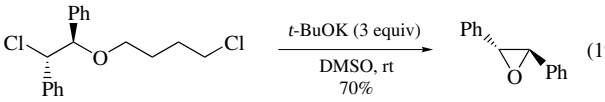


(17)

Oxiranes are obtained by treating β-hydroxy alkylselenonium or β-hydroxy alkylsulfonium salts with *t*-BuOK/DMSO.[32] Although the stereochemistry of the reactant is uncertain, only the *cis*-oxirane is obtained in the reaction shown in eq 18.[32b] An interesting example of oxirane formation involving a fragmentation of a β,δ'-dihalo ether is shown in eq 19.[33]

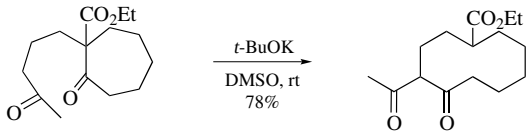


(18)



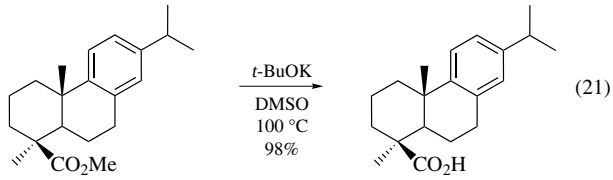
(19)

Upon reaction with *t*-BuOK/DMSO, medium-ring β-keto esters containing 4-oxopentyl side chains undergo three-carbon ring expansion reactions via an aldol–retroaldol process (eq 20).[34] Similar reactions of related cyclic ketones containing electron-withdrawing α-substituents occur in *t*-BuOK/THF.[35]



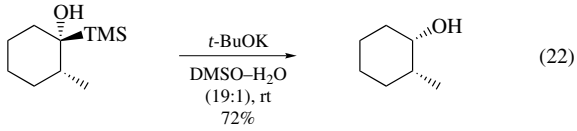
(20)

An interesting modification of the Wolff–Kishner reduction involves the slow addition of a preformed hydrazone to *t*-BuOK/DMSO at rt.[36] However, other modifications of this reduction reaction are more widely used in organic synthesis.[37] *t*-BuOK/DMSO effects O-alkyl cleavage of sterically hindered methyl esters in high yields (eq 21).[38]

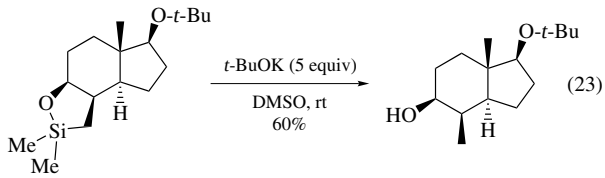


(21)

Protiodesilylations of α- (eq 22) and certain β-hydroxysilanes with *t*-BuOK in wet DMSO occur with retention of configuration.[39] Similar conditions allow protiodesilylations of cyclic saturated (eq 23)[40] and unsaturated siloxanes.[41]



(22)



(23)

Related Reagents. Potassium *t*-Butoxide; Potassium Methoxide–Dimethyl Sulfoxide.

1. Pearson, D. E.; Buehler, C. A., *Chem. Rev.* **1974**, *74*, 45.
2. (a) Bank, S., *J. Org. Chem.* **1972**, *37*, 114. (b) Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: New York, 1988; p 161.
3. Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic: New York, **1965**; Chapter 1 and p 196.
4. (a) Brauman, J. I.; Bryson, J. A.; Kahl, D. C.; Nelson, N. J., *J. Am. Chem. Soc.* **1970**, *92*, 6679. (b) Arnett, E. M.; Venkatasubramanian, K. G., *J. Org. Chem.* **1983**, *48*, 1569.
5. (a) Bartsch, R. A.; Zavada, J., *Chem. Rev.* **1980**, *80*, 453. (b) Krebs, A.; Swienty-Busch, J., *Comprehensive Organic Synthesis* **1991**, *6*, 949.
6. Bartsch, R. A.; Ingram, D. D., *J. Org. Chem.* **1975**, *40*, 3138.
7. (a) Traynham, J. G.; Stone, D. B.; Couvillion, J. L., *J. Org. Chem.* **1967**, *32*, 510. (b) Bartsch, R. A.; Shelly, T. A., *J. Org. Chem.* **1973**, *38*, 2911.
8. Schlosser, M.; An, T. D., *Helv. Chim. Acta* **1979**, *62*, 1194.
9. Binger, P., *Synthesis* **1974**, 190.
10. Trost, B. M.; Hiroi, K.; Kurozumi, S., *J. Am. Chem. Soc.* **1975**, *97*, 438.
11. (a) Veeravagu, P.; Arnold, R. T.; Eigenmann, E. W., *J. Am. Chem. Soc.* **1964**, *86*, 3072. (b) Wood, N. F.; Chang, F. C., *J. Org. Chem.* **1965**, *30*, 2054.
12. Snyder, C. H.; Soto, A. R., *J. Org. Chem.* **1964**, *29*, 742.
13. Chang, F. C., *Tetrahedron Lett.* **1964**, 305.
14. Bharucha, K. R.; Schrenk, H. M., *Experientia* **1965**, *21*, 248.
15. Chang, F. C.; Wood, N. F., *Steroids* **1964**, *4*, 55.
16. (a) Collier, W. L.; Macomber, R. S., *J. Org. Chem.* **1973**, *38*, 1367. (b) Kocienski, P. J., *J. Org. Chem.* **1974**, *39*, 3285.
17. Reese, C. B.; Shaw, A., *J. Chem. Soc., Perkin Trans. 1* **1976**, 890.
18. Bottini, A. T.; Corson, F. P.; Fitzgerald, R.; Frost, K. A., Jr., *Tetrahedron Lett.* **1970**, 4753, 4757.
19. Wittig, G.; Fritze, P., *Justus Liebigs Ann. Chem.* **1968**, *711*, 82.
20. Sahyun, M. R. V.; Cram, D. J., *Org. Synth.* **1965**, *45*, 89; Sahyun, M. R. V.; Cram, D. J., *Org. Synth., Coll. Vol.* **1973**, *5*, 926.

21. (a) Billups, W. E.; Blakeney, A. J.; Chow, W. Y., *J. Chem. Soc., Chem. Commun.* **1971**, 1461. (b) Billups, W. E.; Shields, T. C.; Chow, W. Y.; Deno, N. C., *J. Org. Chem.* **1972**, *37*, 3676. (c) Billups, W. E.; Chow, W. Y., *J. Am. Chem. Soc.* **1973**, *95*, 4099. (d) Shields, T. C.; Billups, W. E., *Chem. Ind. (London)* **1967**, 1999. (e) Shields, T. C.; Billups, W. E.; Kuntz, A. N., *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 209.
22. Ransom, C. J.; Reese, C. B., *J. Chem. Soc., Chem. Commun.* **1975**, 970.
23. Cupas, C. A.; Roach, W. S., *J. Org. Chem.* **1969**, *34*, 742.
24. (a) Krull, I. S.; Arnold, D. R., *Org. Prep. Proced. Int.* **1969**, *1*, 283. (b) Arora, S.; Binger, P.; Köster, R., *Synthesis* **1973**, 146.
25. (a) Price, C. C.; Snyder, W. H., *J. Am. Chem. Soc.* **1961**, *83*, 1773. (b) Wojtowicz, J. A.; Polak, R. J., *J. Org. Chem.* **1973**, *38*, 2061.
26. (a) Shapiro, E. L.; Legatt, T.; Weber, L.; Oliveto, E. P.; Tanabe, M.; Crowe, D. F., *Steroids* **1964**, *3*, 183. (b) Kaneko, C.; Yamada, S.; Sugimoto, A.; Ishikawa, M.; Sasaki, S.; Suda, T., *Tetrahedron Lett.* **1973**, 2339.
27. Birch, A. J.; Graves, J. M. H.; Siddall, J. B., *J. Chem. Soc.* **1963**, 4234.
28. Devaprabhakara, D.; Cardenas, C. G.; Gardner, P. D., *J. Am. Chem. Soc.* **1963**, *85*, 1553.
29. Vanb Dongen, J. P. C. M.; De Jong, A. J.; Selling, H. A.; Montijn, P. P.; Van Boom, J. H.; Brandsma, L., *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1077.
30. Nozaki, H.; Katô, S.; Noyori, R., *Can. J. Chem.* **1966**, *44*, 1021.
31. Kopp, R.; Hanack, M., *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 821.
32. (a) Dumont, W.; Krief, A., *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 350. (b) Kano, S.; Yokomatsu, T.; Shibuya, S., *J. Chem. Soc., Chem. Commun.* **1978**, 785.
33. Dulcere, J. P.; Rodriguez, J., *Synth. Commun.* **1990**, *20*, 1893.
34. Xie, Z.-F.; Suemune, H.; Sakai, K., *J. Chem. Soc., Chem. Commun.* **1988**, 612.
35. (a) Stach, H.; Hesse, M., *Tetrahedron* **1988**, *44*, 1573. (b) Xie, Z.-F.; Suemune, H.; Sakai, K., *Synth. Commun.* **1989**, *19*, 987. (c) Xie, Z.-F.; Sakai, K., *J. Org. Chem.* **1990**, *55*, 820.
36. Cram, D. J.; Sahyun, M. R. V.; Knox, G. R., *J. Am. Chem. Soc.* **1962**, *84*, 1734.
37. Hutchins, R. O.; Hutchins, M. K., *Comprehensive Organic Synthesis* **1991**, *8*, 327.
38. (a) Chang, F. C.; Wood, N. F., *Tetrahedron Lett.* **1964**, 2969. (b) Welch, S. C.; Hagan, C. P.; Kim, J. H.; Chu, P. S., *J. Org. Chem.* **1977**, *42*, 2879.
39. Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K., *J. Am. Chem. Soc.* **1982**, *104*, 6809.
40. Stork, G.; Sofia, M. J., *J. Am. Chem. Soc.* **1986**, *108*, 6826.
41. Tamao, K.; Maeda, K.; Yamaguchi, T.; Ito, Y., *J. Am. Chem. Soc.* **1989**, *111*, 4984.

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Potassium Hydroxide–Dimethyl Sulfoxide

KOH–Me_2SO

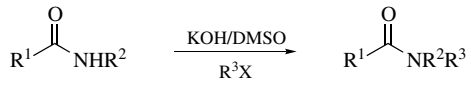
(KOH)
[1310-58-3] HKO (MW 56.11)
InChI = 1/K.H2O/h;1H2/q+1;/p-1/fK.HO/h;1h/qm;-1
InChIKey = KWYUFKZDYYNOTN-GDVMLVAHCS

(DMSO)
[67-68-5] C_2H_6OS (MW 78.15)
InChI = 1/C2H6OS/c1-4(2)3/h1-2H3
InChIKey = IAZDPXIOMUYVGZ-UHFFFAOYAR

(very strong base; low nucleophilicity due to low solubility which allows only surface reactivity[2])

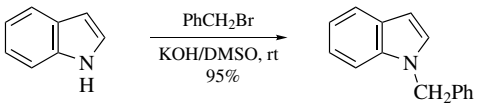
Physical Data: see entries for potassium hydroxide and dimethyl sulfoxide; KOH/DMSO has pK_a of 27 or higher.[1]

Alkylation of Amides, Phenols, Alcohols, and Acids. A variety of carboxamides were alkylated with primary alkyl halides using KOH in DMSO to give the *N*-alkyl amides (eq 1) in 54–90% yield. Most reactions were carried out at rt, but in some cases heating to 90 °C was required.[3] Similar conditions were applied to alcohols, phenols, and acids to form ethers and esters.[4] The procedure applies to MeI and all primary halides. Secondary alkyl halides show evidence of competitive dehydrohalogenation, while tertiary halides do not give any alkylation products. The procedure was applied to the *N*- and *O*-permethylation of peptides.[4] It was also applied to the methylation of hydroxypyridines in 39–78% yield.[5] In all the above cases, the substrate and alkyl halide were added to powdered KOH in DMSO and stirred at rt. It was unnecessary to use especially dry DMSO or to protect the reaction mixture from atmospheric moisture.



(1)

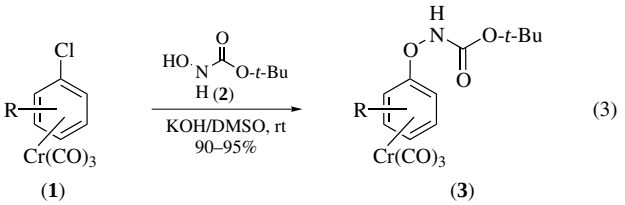
***N*-Alkylation of Indoles and Pyrroles.** *N*-Alkyl indoles and pyrroles were prepared in high yields (85–95%) by reaction of indoles and pyrroles with primary alkyl halides in DMSO and powdered KOH at rt (eq 2). The yields were lower with secondary halides (60% for *N*-isopropylindole), while tertiary halides gave no alkylation products.[6]



(2)

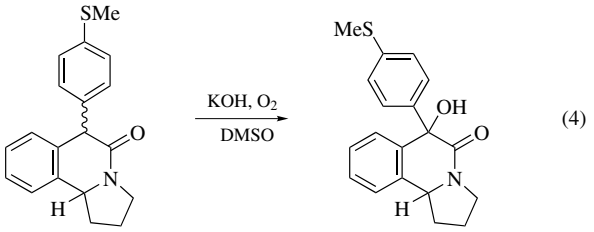
Alkylation of Ketones. Ketones can be permethylated with iodomethane in DMSO containing solid KOH. Cyclobutanone, cyclopentanone, and indanone gave the corresponding tetramethyl ketones in 49, 90, and 75% yields, respectively. All reagents can be used without drying and KOH can be used as pellets or as a powder.[2]

Synthesis of *O*-Arylhydroxylamines. Reaction of tricarbonylchromium complexes of aryl halides (**1**) with *N*-*t*-butoxycarbonylhydroxylamine (**2**) in DMSO and powdered KOH under N_2 at rt resulted in the nucleophilic substitution of the Cl to give the corresponding tricarbonyl[(*t*-butoxycarbonylaminoxy)arene]chromium complexes (**3**) (eq 3). Consecutive I_2 treatment and acid hydrolysis gave the *O*-arylhydroxylamines in high overall yields.[7]



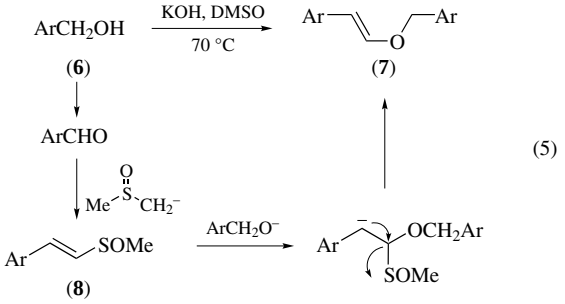
(1) (3) (3)

Hydroxylation of Ketones. Treatment of the ketone (**4**) with KOH in warm DMSO in the presence of O_2 followed by the in situ reduction of the intermediate hydroperoxide with dithionite gave (**5**) as a 1:1 mixture of diastereomers (eq 4).[8]



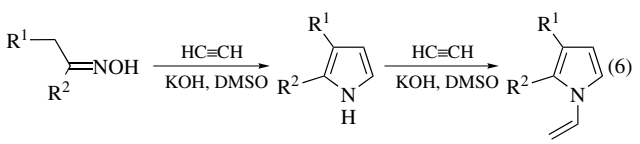
(4) (5)

Synthesis of (*E*)-β-(Benzyloxy)styrenes from Benzyl Alcohols. (*E*)-β-(Benzyloxy)styrenes (**7**) were obtained from the reaction of benzyl alcohols (**6**) with KOH/DMSO (eq 5) in 56–92% yields. This result was explained by an initial oxidation to the benzaldehyde followed by a condensation with DMSO anion to form intermediate (**8**). Subsequent addition of benzyloxide anion to (**8**) and elimination of $MeSO^-$ gives the product (**7**). The incorporation of the DMSO carbon was confirmed by ^2H and ^{13}C labelling. The methyl styryl sulfoxide intermediate (**8**) was independently synthesized and converted into (**7**) under identical reaction conditions.[9]



(6) (7) (8) (5)

Preparation of *N*-Vinylpyrroles. The reaction of ketoximes having at least one α-CH_2 group with acetylene in DMSO/KOH at 80–120 °C under atmospheric pressure gave *N*-vinylpyrroles in average yields of 70–80% via an intermediate pyrrole (eq 6). The conditions are also suitable for *N*-vinylation of pyrroles and other NH heterocycles in good yields.[1b]



(6)

1. For discussions of the behavior of KOH in polar aprotic solvents see (a) Jolly, W. L., *J. Chem. Educ.* **1967**, *44*, 304. (b) Trofimov, B. A., *Russ. Chem. Rev. (Engl. Transl.)* **1981**, *50*, 138 and references therein.
2. Langhals, E.; Langhals, H., *Tetrahedron* **1990**, *31*, 859 and references therein.
3. Isele, G. L.; Lüttringhaus, A., *Synthesis* **1971**, 266.
4. Johnstone, R. A. W.; Rose, M. E., *Tetrahedron* **1979**, *35*, 2169.
5. Finkentey, C.; Langhals, E.; Langhals, H., *Chem. Ber.* **1983**, *116*, 2394.
6. Heaney, H.; Ley, S. V., *J. Chem. Soc., Perkin Trans. 1* **1973**, 499.
7. Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S., *Synthesis* **1988**, 344.
8. Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E., *J. Am. Chem. Soc.* **1990**, *112*, 3567.
9. Langhals, H.; Julia, M.; Uguen, D., *Liebigs Ann. Chem.* **1982**, 2216.

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Potassium Monoperoxysulfate

$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$

[37222-66-5] $H_3K_5O_{18}S_4$ (MW 614.81)

InChI = 1/5K.2H2O5S.2H2O4S/c;;;;;2*1-5-6(2,3)4;2*1-5(2,3)4/h;;;;;2*1H,(H,2,3,4);2*(H2,1,2,3,4)/q5*+1;;;;/p-5/f5K.2HO5S.HO4S.O4S/h;;;;;2*1h,2H;1H;/q5m;3*-1;-2

InChIKey = HJKYXKSLRZKNSI-QZKRTAEBCM

(oxidizing agent for a number of functional groups, including alkenes,[16] arenes,[17] amines,[26] imines,[30] sulfides;[37] used for the preparation of dioxiranes[5])

Alternate Names: potassium caroate, potassium hydrogen persulfate, Oxone®, potassium peroxymonosulfate.

Physical Data: mp dec; *d* 1.12–1.20 g cm^{-3}.

Solubility: sol water (25.6 g 100 g, 20 °C), aqueous methanol, ethanol, acetic acid; insol common organic solvents.

Form Supplied in: white, granular, free flowing solid. Available as Oxone®and as Curox®and Caroat®.

Analysis of Reagent Purity: iodometric titration, as described in the Du Pont data sheet for Oxone®.

Handling, Storage, and Precautions: the Oxone triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ is a relatively stable, water-soluble form of potassium monopersulfate that is convenient to handle and store. Oxone has a low order of toxicity, but is irritating to the eyes, skin, nose, and throat. It should be used with adequate ventilation and exposure to its dust should be minimized. Traces of heavy metal salts catalyze the decomposition of Oxone. For additional handling instructions, see the Du Pont data sheet.

Original Commentary

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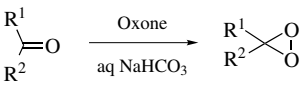
Indiana University, Bloomington, IN, USA

Oxidation Methodology. Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is a convenient, stable source of potassium monopersulfate

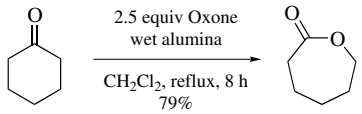
(caroate), which serves as a stoichiometric oxidizing agent under a variety of conditions. Thus aqueous solutions of Oxone can be used to perform oxidations in homogeneous solution and in biphasic systems using an immiscible cosolvent and a phase-transfer catalyst. Recently, solid–liquid processes using supported Oxone reagents have been developed. Other oxidation methods involve the generation and reaction of a secondary reagent under the reaction conditions, as with the widely employed aqueous Oxone–ketone procedures, which undoubtedly involve dioxirane intermediates.[1–4] In other instances, oxaziridine derivatives and metal oxo complexes appear to be the functional oxidants formed in situ from Oxone. Synthetically useful examples of these oxidations are grouped below according to the functional groups being oxidized.

Ketones and Other Oxygen Functions. Various ketones can be converted to the corresponding dioxiranes by treatment with buffered aqueous solutions of Oxone (eq 1). Of particular interest are dimethyldioxirane[5] ($R^1 = R^2 = Me$) and methyl(trifluoromethyl)dioxirane[6] ($R^1 = Me$, $R^2 = CF_3$) derived from acetone and 1,1,1-trifluoro-2-propanone, respectively. The discovery of a method for the isolation of dilute solutions of these volatile dioxiranes in the parent ketone by codistillation from the reaction mixture has opened an exciting new area of oxidation chemistry. Solutions of dioxiranes derived from higher molecular weight ketones have also been prepared.[5,7]



(1)

Interestingly, the reaction of a solid slurry of Oxone and wet alumina with solutions of cyclic ketones in CH_2Cl_2 provokes Baeyer–Villiger oxidation to give the corresponding lactones (eq 2).[8] The same wet alumina–Oxone reagent can be used to oxidize secondary alcohols to ketones (eq 3).[9] Aldehydes are oxidized to acids by aqueous Oxone.[5,10]



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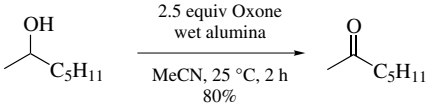
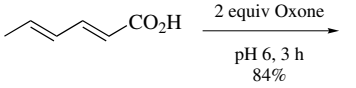


(3)

Alkenes, Arenes, and Alkanes. Aqueous solutions of Oxone can epoxidize alkenes which are soluble under the reaction conditions; for example, sorbic acid (eq 4)[11] (the high selectivity for epoxidation of the 4,5-double bond here is noteworthy). Alternatively, the use of a cosolvent to provide homogeneous solutions promotes epoxidation (eq 5).[11] Control of the pH to near neutrality is usually necessary to prevent hydrolysis of the epoxide. Rapidly stirred heterogeneous mixtures of liquid alkenes and aqueous Oxone solutions buffered with $NaHCO_3$ also produce epoxides, as shown in eq 6.[12]



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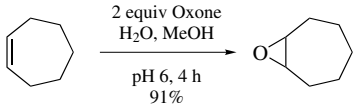

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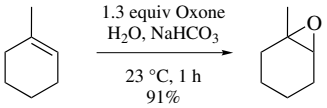
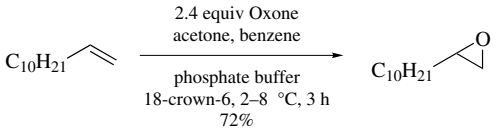


(6)

An in situ method for epoxidations with dimethyldioxirane using buffered aqueous acetone solutions of Oxone has been widely applied.[1–4] The epoxidation of 1-dodecene is particularly impressive in view of the difficulty generally encountered in the epoxidation of relatively unreactive terminal alkenes (eq 7).[13] A biphasic procedure using benzene as a cosolvent and a phase-transfer agent was utilized in this case. Equally remarkable is the epoxidation of the methylenecyclopropane derivatives indicated in eq 8, given the propensity of the products to rearrange to the isomeric cyclobutanones.[14]



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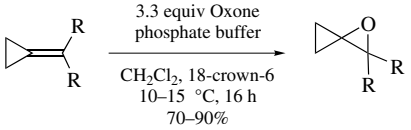
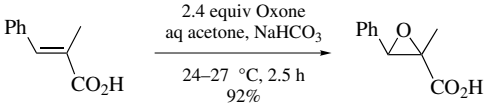
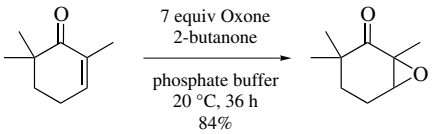


(8)

The epoxidation of conjugated double bonds also proceeds smoothly with the Oxone–acetone system, as illustrated by eq 9.[15] The conversion of water-insoluble enones can be accomplished with this method using CH_2Cl_2 as a cosolvent and a quaternary ammonium salt as a phase-transfer catalyst. However, a more convenient procedure utilizes 2-butanone both as a dioxirane precursor and as an immiscible cosolvent (eq 10).[16] No phase-transfer agent is required in this case.

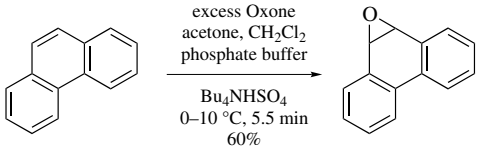


(9)



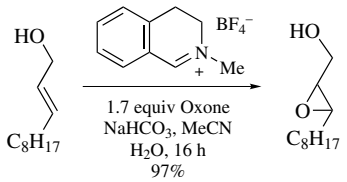
(10)

The epoxides of several polycyclic aromatic hydrocarbons have been prepared by the use of a large excess of oxidant in a biphasic Oxone–ketone system under neutral conditions, as shown for the oxidation of phenanthrene (eq 11).[17] However, the use of isolated dioxirane solutions is more efficient for the synthesis of reactive epoxides, since hydrolysis of the product is avoided.[5,18] A number of unstable epoxides of various types have been produced in a similar manner, as discussed for dimethyldioxirane and methyl(trifluoromethyl)dioxirane.

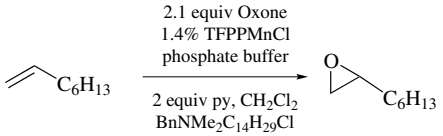


(11)

Epoxidations have also been performed with other oxidizing agents generated in situ from Oxone. An intriguing method uses a catalytic amount of an immonium salt to facilitate alkene epoxidation in a process which apparently involves an intermediate oxaziridium species as the active oxidant.[19] This procedure is carried out by adding solid Oxone and $NaHCO_3$ to a solution of the alkene and catalyst in MeCN containing a very limited quantity of water (eq 12). Finally, Oxone is the stoichiometric oxidant in interesting modifications of the widely studied metal porphyrin oxidations, where it has obvious advantages over some of the other oxidants commonly used.[20] The potential of this method is illustrated by the epoxidation reaction in eq 13.[21] In this conversion, only 1.4 mol % of the robust catalyst tetrakis(pentafluorophenyl)porphyrinatomanganese chloride (TFPPMnCl) is required. The catalytic hydroxylation of unactivated hydrocarbons is also possible (eq 14).[22] Other metal complexes promote similar oxidations.[23–25]



(12)



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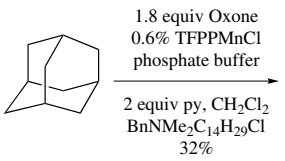
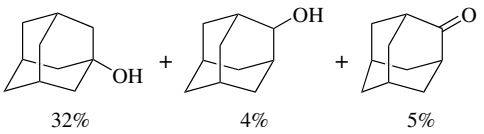
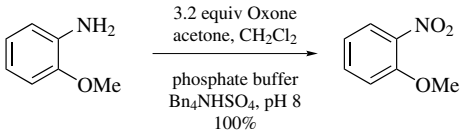


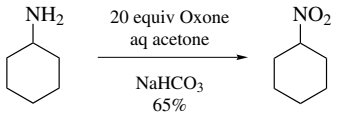


(14)

Nitrogen Compounds. The aqueous Oxone–acetone combination has been developed for the transformation of certain anilines to the corresponding nitrobenzene derivatives, as exemplified in eq 15.[26] This process involves sequential oxidation steps proceeding by way of an intermediate nitroso compound. In the case of primary aliphatic amines, other reactions of the nitrosoalkane species compete with the second oxidation step (for example, dimerization and tautomerization to the isomeric oxime), thereby limiting the synthetic generality of these oxidations.[27] An overwhelming excess of aqueous Oxone has been used to convert cyclohexylamine to nitrocyclohexane (eq 16).[27]

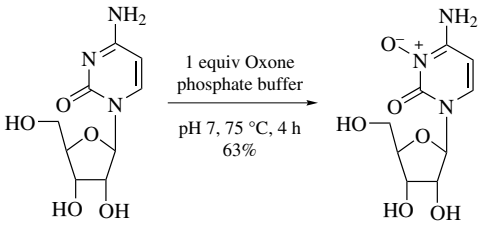


(15)



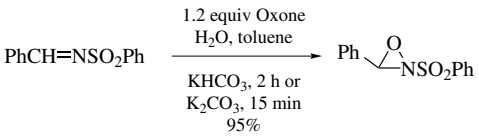
(16)

Pyridine is efficiently converted to its *N*-oxide by the Oxone–acetone oxidant.[5] Cytosine and several of its derivatives give the *N3*-oxides selectively upon reaction with buffered Oxone (eq 17).[28] A similar transformation of adenosine 5′-monophosphate yields the *N1*-oxide.[29]



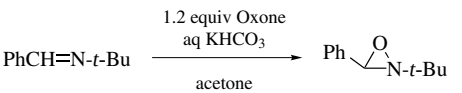
(17)

The very useful *N*-sulfonyloxaziridines are conveniently prepared by treating *N*-sulfonylimines with Oxone in a biphasic solvent system (eq 18).[30,31] Either bicarbonate or carbonate can be used to buffer this reaction, but reaction is much faster with carbonate, suggesting that the monopersulfate dianion is the oxidizing species (for illustrations of the remarkable chemistry of these oxaziridines, see *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine).

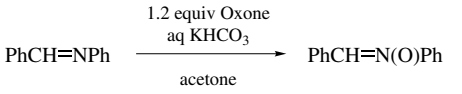


(18)

The Oxone–acetone system has also been employed for the synthesis of simple oxaziridines from *N*-alkylaldimines (eq 19).[32] Interestingly, the *N*-phenyl analogs produce the isomeric nitrones rather than the oxaziridines (eq 20). It is noteworthy that MeCN can replace acetone as the solvent in this procedure.

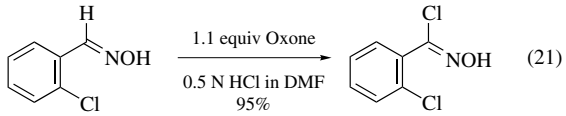


(19)



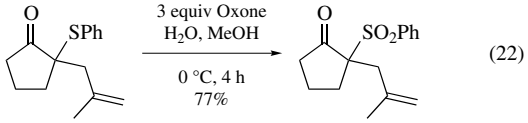
(20)

Finally, the chlorination of aldoximines gives the corresponding hydroximoyl chlorides, as shown in eq 21.[33] The combination of Oxone and anhydrous HCl in DMF serves as a convenient source of hypochlorous acid, the active halogenating agent.



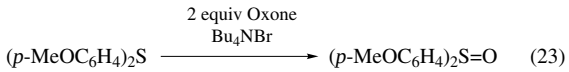
(21)

Sulfur Compounds. Some of the earliest applications of Oxone in organic synthesis involved the facile oxidation of sulfur functions. For example, aqueous Oxone selectively oxidizes sulfides to sulfones even in highly functionalized molecules, as illustrated in eq 22.[34] Sulfones can also be prepared by a convenient two-phase system consisting of a mixture of solid Oxone, 'wet' montmorillonite K10 clay, and a solution of the sulfide in an inert solvent.[35]

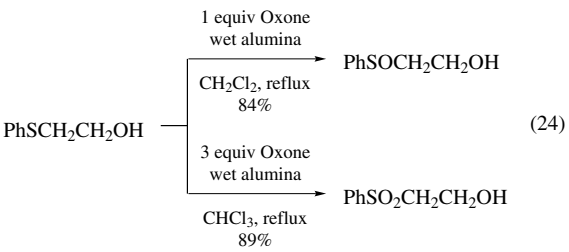


(22)

The partial oxidation of sulfides to sulfoxides has been accomplished in a few cases by careful control of the reaction stoichiometry and conditions.[34] A biphasic procedure for sulfoxide formation from diaryl sulfides is shown in eq 23.[36] However, a more attractive and versatile procedure uses a solid Oxone–wet alumina reagent with a solution of the sulfide.[37] This method permits control of the reaction to form either the sulfoxide or the sulfone simply by adjusting the amount of oxidant and the reaction temperature, as illustrated in eq 24. These oxidations are compatible with other functionality.

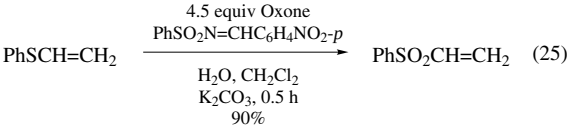


(23)



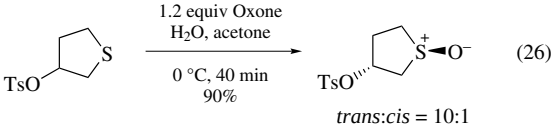
(24)

Another intriguing method for the selective oxidation of sulfides to sulfoxides (eq 25) uses buffered Oxone in a biphasic solvent mixture containing a catalytic amount of an *N*-phenylsulfonylimine as the precursor of the actual oxidizing agent, the corresponding *N*-sulfonyloxaziridine.[38] The oxaziridine is smoothly and rapidly formed by reaction of the imine with buffered Oxone and regenerates the imine upon oxygen transfer to the sulfide. The greater reactivity of the sulfide relative to the sulfoxide accounts for the preference for monooxidation in this procedure. The biphasic nature of this reaction prevents direct oxidation by Oxone, which would be less selective.



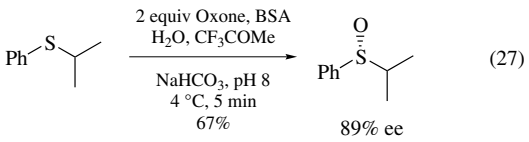
(25)

Oxone sulfoxidations can show appreciable diastereoselectivity in appropriate cases, as demonstrated in eq 26.[39] Enantioselective oxidations of sulfides to sulfoxides have been achieved by buffered aqueous Oxone solutions containing bovine serum albumin (BSA) as a chiral mediator (eq 27).[40] As little as 0.05 equiv of BSA is required and its presence discourages further oxidation of the sulfoxide to the sulfone. Oxone can be the active oxidant or reaction can be performed in the presence of acetone, trifluoroacetone, or other ketones, in which case an intermediate dioxirane is probably the actual oxidizing agent. The level of optical induction depends on structure of the sulfide and that of any added ketone. Sulfoxide products show ee values ranging from 1% to 89%, but in most examples the ee is greater than 50%.



(26)

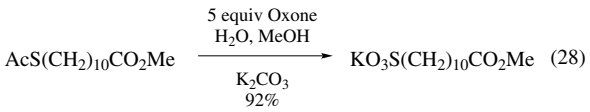
trans:*cis* = 10:1



(27)

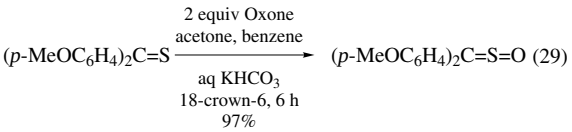
89% ee

1-Decanethiol is efficiently oxidized to decanesulfonic acid (97% yield) by aqueous Oxone.[10] In a similar manner an acylthio function was converted into the potassium sulfonate salt, as shown in eq 28.[41]



(28)

Finally, certain relatively stable thioketones can be transformed into the corresponding thione *S*-oxides by the aqueous Oxone–acetone reagent (eq 29).[42]



(29)

First Update

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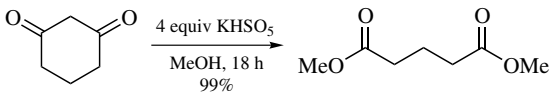
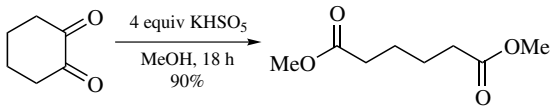
Modification of Oxone. Since Oxone is a triple salt ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) only about 50% per mole is active oxidant. A convenient method for the preparation of purified

$KHSO_5 \cdot H_2O$ on a large scale has been developed which allows for significant reduction in the amount of oxidizing agent needed for a reaction.[43] One of the main drawbacks of using Oxone is that aqueous/alcoholic or at least biphasic reaction conditions are usually necessary. To circumvent this problem several organic-soluble forms of Oxone have been developed including tetra-*n*-butylammonium peroxymonosulfate (n-Bu_4NHSO_5),[44] tetraphenylphosphonium peroxymonosulfate (Ph_4PHSO_5),[45,46] and benzyltriphenylphosphonium peroxymonosulfate ($BnPh_3PHSO_5$).[47] These oxidants can be used under anhydrous conditions and in many cases show similar reactivity to Oxone. A study has been done comparing the activity of these different oxidants in the oxidation of benzaldehyde, *trans*-stilbene, triphenylphosphine, thioanisole, and phenylboronic acid.[43]

Ketones, Aldehydes, and Alcohols. The well-known Baeyer-Villiger oxidation of ketones by Oxone (eq 2) has been exploited in a variety of reactions. This protocol has been used with $KHSO_5$ for cleavage of α- and β-dicarbonyl compounds to esters or acids (eqs 30 and 31).[48,49] This process is simpler, cheaper, and milder than the commonly used haloform reaction.

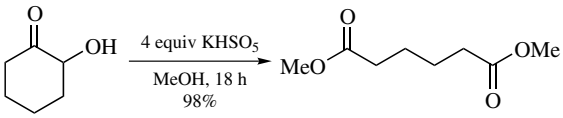


(30)



(31)

α-Hydroxy- and α-nitroketones are oxidatively cleaved by Oxone in a similar manner to yield the corresponding esters and acids (eqs 32 and 33).[48–50] α-Nitroketones can be cleaved to dicarboxylic acids or dicarboxylic acid monomethyl esters depending on reaction conditions. It is proposed that in the case of α-hydroxy ketones Bayer-Villiger oxidation is followed by oxidation of the resulting aldehyde to give the diacid/ester.



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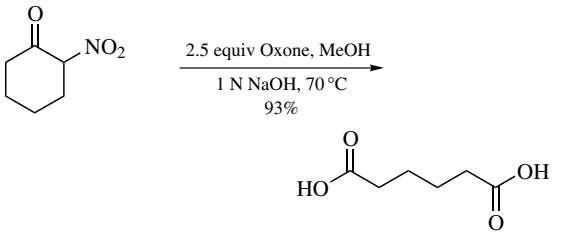
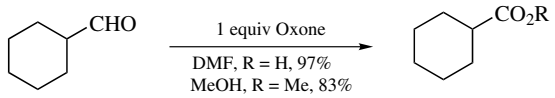


(33)

Oxone has also been recently more thoroughly studied as reagent for the oxidation of aldehydes.[51,52] Aryl- and aliphatic aldehydes can be efficiently converted directly to acids or esters depending on the choice of solvent (eq 34).[52] They can also be converted to nitriles in one pot by reaction with hydroxylamine on alumina with microwave irradiation (eq 35).[53]



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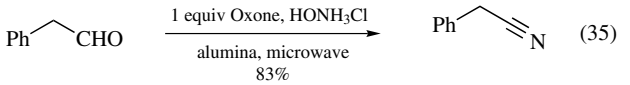
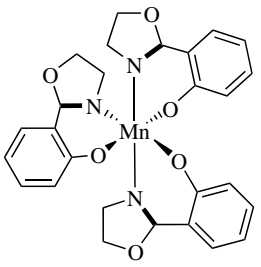


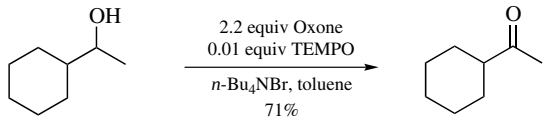
(35)

Oxone oxidizes metal complexes including tris[(2-oxazolinyl)-phenolato] manganese(III) which, in conjunction with n-Bu_4NBr, is an effective oxidant for aromatic and primary and secondary aliphatic alcohols.[54]

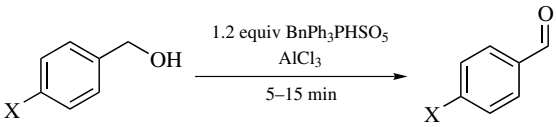


tris[(2-oxazolinyl)phenolato] manganese(III)

Additionally, Oxone is a suitable stoichiometric oxidant for alcohol oxidations with TEMPO and n-Bu_4NBr even in aprotic solvents (eq 36).[55] Aliphatic and electron-rich benzylic alcohols give lower yields than electron-neutral benzylic alcohols in this case. A simple combination of Oxone and NaBr can oxidize benzylic alcohols to aldehydes and ketones.[56] Once again, electron-rich benzylic alcohols gave lower yields; in this case it is due to competing halogenation of the aromatic ring. $BnPh_3PHSO_5$ has also been used with $AlCl_3$ to oxidize benzylic and allylic alcohols under aprotic solvent-free conditions (eq 37).[57] This protocol gives high yields for both electron-poor and electron-rich primary and secondary benzylic alcohols.



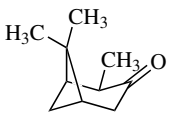
(36)



(37)

X = NO_2, 100%
X = OMe, 80%

Alkenes, Alkynes, Arenes, and Alkanes. One of the most common applications of Oxone in organic synthesis is the in situ formation of dioxiranes from ketones (eq 1). Dioxirane chemistry has grown significantly in recent years, particularly in the area of enantioselective epoxidation, and a wide variety of chiral ketones have been designed for this purpose.[58–69] Notably, ketones (**5** and **6**) derived from fructose and glucose, respectively, have been shown to be effective catalysts for enantioselective epoxidations of a variety of *trans*-, trisubstituted, *cis*-, and terminal olefins with Oxone as primary oxidant (eqs 38 and 39).[70–72]



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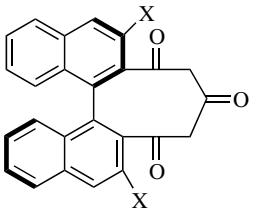

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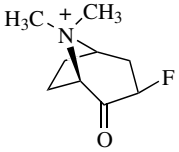

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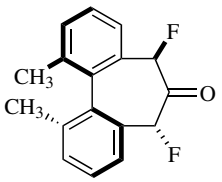

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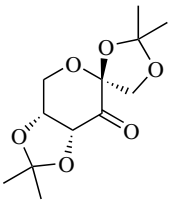

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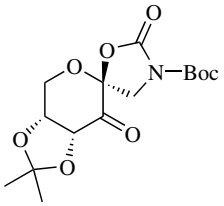

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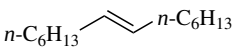
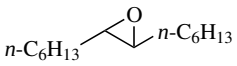


1.4 equiv Oxone, 0.3 equiv **5**
CH_3CN, H_2O, K_2CO_3
pH 9.3, −10 °C
89%, 95% ee



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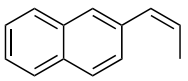
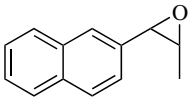


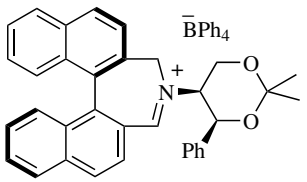
1.8 equiv Oxone, 0.15 equiv **6**
DME/DMM, H_2O, K_2CO_3
pH 8, 0 °C
91%, 92% ee



(39)

Oxone and its derivatives have also been used with chiral iminium salts and amines to form enantiomerically enriched epoxides. The scope and enantioselectivity of epoxidation with chiral iminium salts with Oxone and Ph_4PHSO_5 have made progress during recent years.[46,73–77] Chiral iminium salts (**7** and **8**) have been particularly successful for various olefins (eqs 40 and 41).[78,79]

Amine-catalyzed epoxidation is a relatively new area, and the active species is thought to be an ammonium peroxymonosulfate salt which acts as a phase transfer catalyst and undergoes electrophilic attack by an olefin.[80–82] Use of chiral amines has given rise to enantiomerically enriched epoxides (eq 42).



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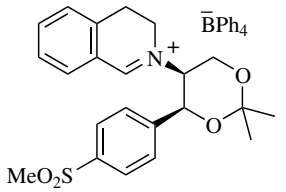

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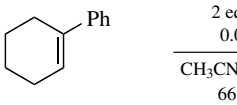
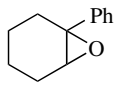


2 equiv Oxone
0.05 equiv **7**
CH_3CN, H_2O, Na_2CO_3
66%, 88% ee



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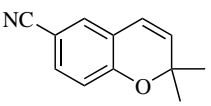
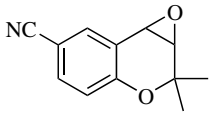


2 equiv Ph_4PHSO_5
0.1 equiv **8**
$CHCl_3$, −40 °C
59%, 97% ee



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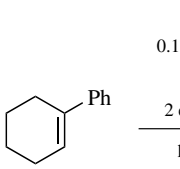
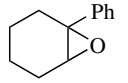
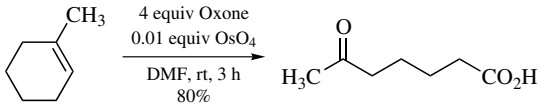


2 equiv Oxone, $NaHCO_3$
pyridine, CH_3CN, H_2O
93%, 46% ee



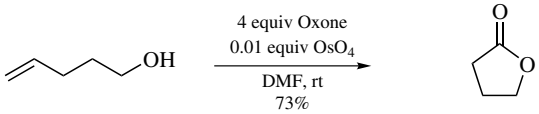
(42)

Oxone in conjunction with OsO_4 cleaves alkenes to ketones or carboxylic acids (eq 43).[83] This protocol has the advantage over traditional methods in that there is no need for intermediate 1,2-diols. This method has been exploited in the direct synthesis of lactones from alkenols (eq 44) and tetrahydrofuran-diols from 1,4-dienes as well.[84,85]



4 equiv Oxone
0.01 equiv OsO_4
DMF, rt, 3 h
80%

(43)

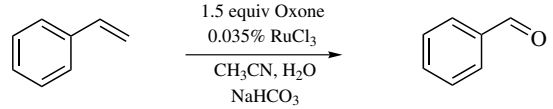


4 equiv Oxone
0.01 equiv OsO_4
DMF, rt
73%

(44)

When used in conjunction with $RuCl_3$, Oxone cleaves alkenes to aldehydes in high yields (eq 45).[86] This method is less effective for aliphatic olefins, and $NaIO_4$ is suggested as an alternate oxidant in these cases. The same combination with more Oxone and less water oxidizes alkenes to α-hydroxy ketones (eq 46).[87,88] The reaction is fairly regioselective depending on the electronic properties of the substrate, with the hydroxy group preferentially ending up next to the more electron-withdrawing substituent. 1,2-Diols, which are the possible intermediates/by-products in the above keto-hydroxylation, are also oxidized under the same conditions to α-hydroxy ketones, and enantiopurity of the starting materials is preserved during the reaction (eq 47).[89] Oxone in

aqueous acetone has been shown to dihydroxylate various 1,2-glycals in one step in moderate to good yields.[90]



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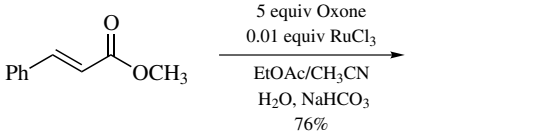
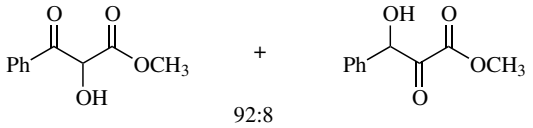
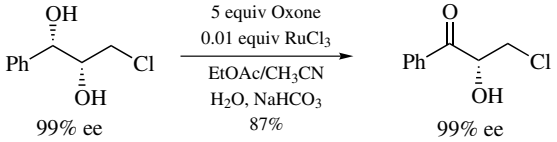


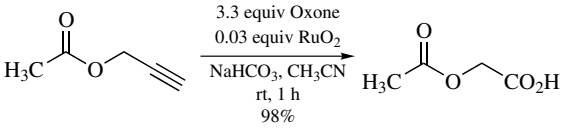


(46)



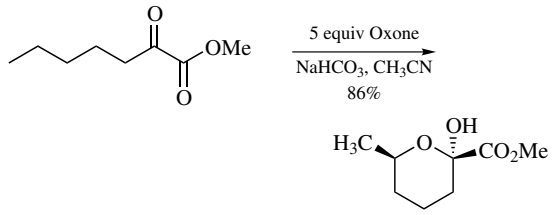
(47)

Oxone, in conjunction with RuO_2, cleaves alkynes to carboxylic acids.[91] Both internal and terminal alkynes are cleaved in short reacton times with high yields (eq 48). Intermediate 1,2-diketones are proposed.



(48)

Dioxiranes generated from Oxone have recently been shown to undergo C–H insertion reactions with activated and unactivated C–H bonds. This strategy has been used in an intramolecular fashion for the oxidation of hydrocarbons (eq 49) and steroids.[92,93] Fructose-derived ketone (**5**) has also been used for this purpose in an intermolecular reaction for the desymmetrization and kinetic resolution of 1,2-diols to α-hydroxy ketones (eq 50).[94,95] There has also been a report of the direct oxidation of hydrocarbons to ketones and lactones by Mn-porphyrin complexes with Oxone.[96]



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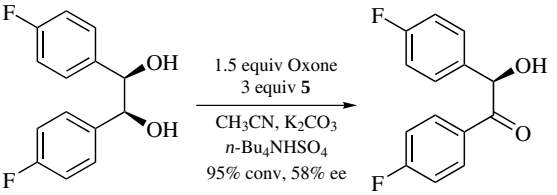
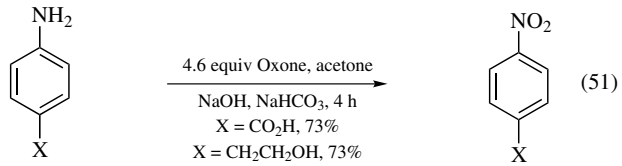


(50)

Nitrogen Compounds. Previous methods for oxidizing anilines to nitro compounds with Oxone/acetone were ineffective with carboxylic acid and alcohol-containing systems.[26] A new method using Oxone and acetone under totally aqueous conditions allows oxidation of carboxylic and alcoholic anilines as well (eq 51).[97] In this case the reaction occurred in the absence of acetone but yields were significantly lower. The combination of Oxone and ozone has been used to oxidize amino sugars to nitro sugars as well (eq 52).[98]



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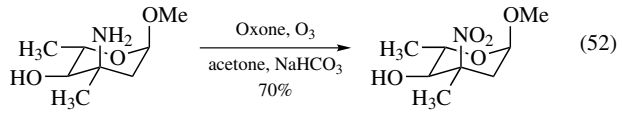
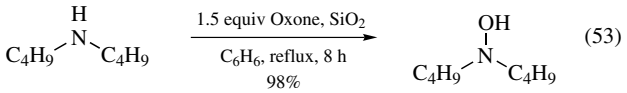


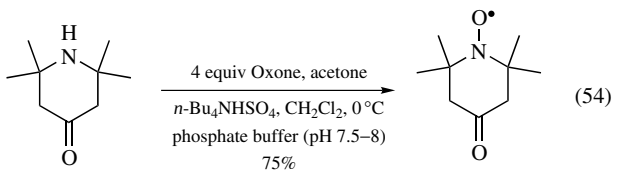
(52)

Oxone adsorbed on silica gel or alumina is a very effective oxidant for the selective oxidation of primary and secondary amines to hydroxylamines without overoxidation. These reactions can even be accomplished under solvent-free conditions and with very short reaction times with heating or microwave irradiation (eq 53).[99] Pyridine and trialkylamines were also readily oxidized to their *N*-oxides. It is suggested that the hydroxylamines are protected from overoxidation because of their strong adsorption to the silica gel or alumina surface.



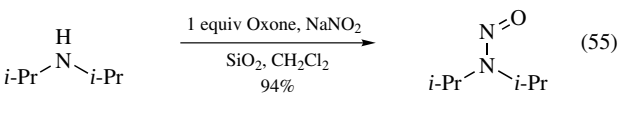
(53)

The Oxone/acetone system is also very effective for the formation of nitroxides from secondary amines without α-hydrogens (eq 54).[100]

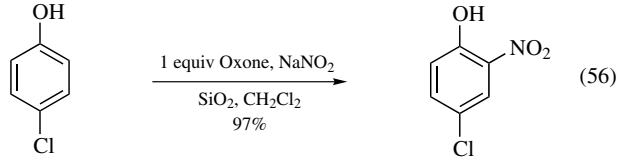


(54)

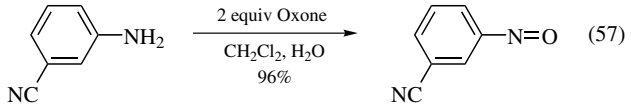
Because of Oxone's acidic nature, *N*-nitrosation of secondary amines is possible with the use of sodium nitrite in the presence of wet SiO_2 (eq 55).[101] Nitrophenols can be obtained via nitrosation-oxidation of phenols under similar conditions (eq 56).[102] Although acidic, the use of Oxone for these reactions eliminates the need for strong acids to generate NO^+ unlike traditional methods. Nitrosoarenes can also be prepared by oxidation of anilines with Oxone (eq 57).[103]



(55)

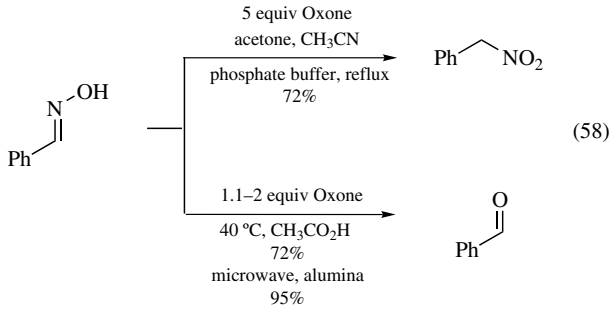


(56)



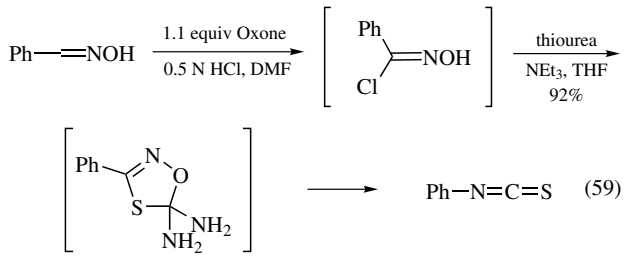
(57)

Oximes can be converted to their corresponding nitro compounds with Oxone and refluxing acetonitrile (eq 58).[104] They can also be cleaved to their parent carbonyl compounds by Oxone in conjunction with glacial acetic acid, or silica gel/alumina and microwave irradiation (eq 58).[105–107] Ketoximes and aldoximes are both converted to carbonyl compounds in high yields using the microwave and alumina procedure. Several of the above transformations are highlighted in the oxidative decarboxylation of α-amino acids to form ketones and carboxylic acids.[108]



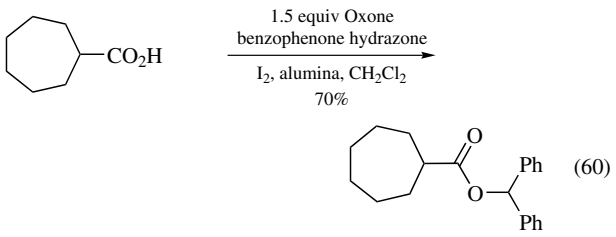
(58)

Aldoximes can be converted to isothiocyanates in a convenient one-pot procedure with Oxone and HCl based on a procedure for synthesizing hydroximoyl chlorides.[33,109] The reaction presumably proceeds through an oxathiazoline that decomposes to give the isothiocyanate (eq 59).

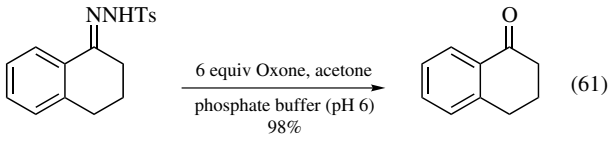


(59)

An interesting method for the protection of carboxylic acids as diphenylmethyl esters in high yield using Oxone and benzophenone hydrazone has been reported (eq 60).[110] Various aromatic tosylhydrazones can also be cleaved to carbonyl compounds by Oxone/acetone (eq 61).[111] It is proposed that cleavage occurs via collapse of an oxaziridine intermediate. $BnPh_3PHSO_5$ has been used with $BiCl_3$ to regenerate carbonyl compounds from oximes, phenylhydrazones, 2,4-dinitrophenylhydrazones, and semicarbazones under nonaqueous conditions.[112] Yields are generally very good, and it is reported that it is also possible to oxidize alcohols to ketones under these conditions without affecting any of the above mentioned carbonyl derivatives.

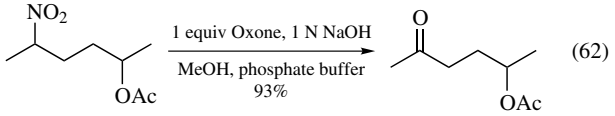


(60)



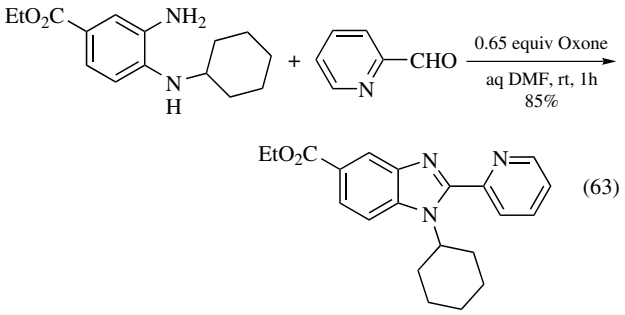
(61)

Likewise, Oxone is useful for the conversion of nitro groups into carbonyl compounds (Nef reaction) in the presence of aqueous base (eq 62).[113]



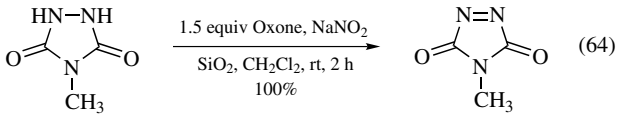
(62)

Benzimidazoles can be synthesized in one step by condensing 1,2-phenylenediamines and aldehydes in the presence of Oxone (eq 63).[114] The reaction gives good selectivity and tolerates electron-rich and electron-poor phenylenediamines as well as a wide variety of aromatic and aliphatic aldehydes.



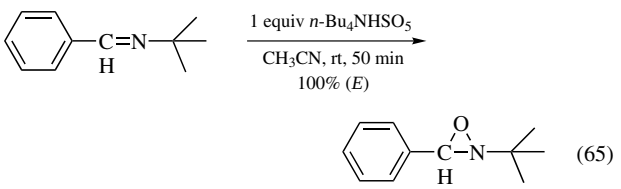
(63)

Urazoles are oxidized to triazolinediones when subjected to Oxone and $NaNO_2$ (eq 64).[115] These compounds, which have typically been difficult to synthesize and purify, are relatively easily made in high yields and purity by this procedure.



(64)

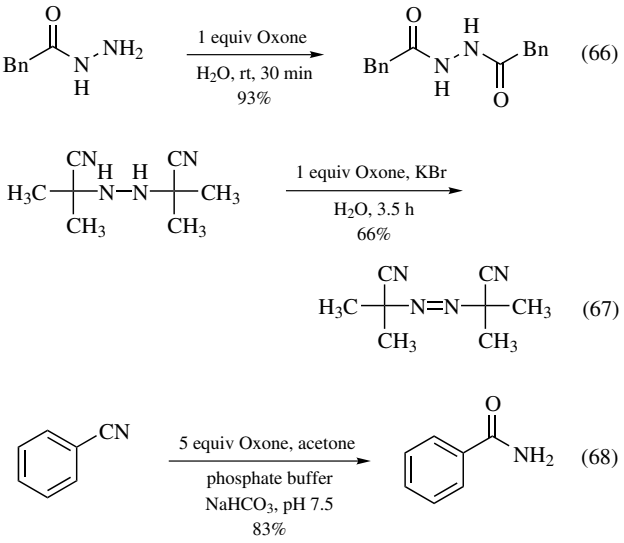
Oxaziridines, which have previously been produced from reaction of imines with Oxone,[30,31] have recently been made in excellent yields with n-Bu_4NHSO_5 in acetonitrile (eq 65).[116] The reactions are generally *E*-selective. However, as the size of the group on nitrogen decreases more *Z*-isomer is produced. The effects of solvent and Lewis acids on the *E*/*Z*selectivity and rate of reaction were studied as well.



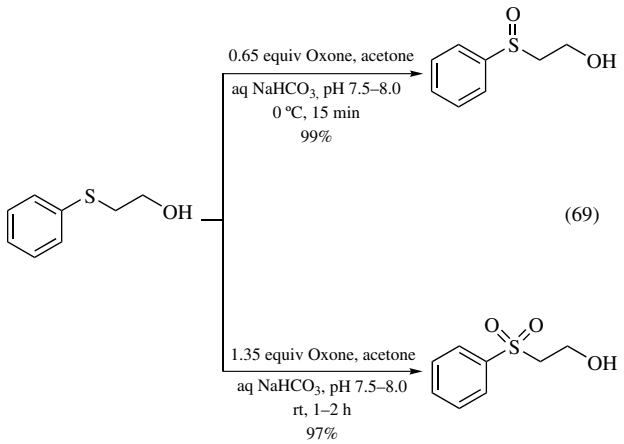
(65)

Acylhydrazides are oxidized to *N,N′*-diacylhydrazines in high yields with aqueous Oxone (eq 66), although only aromatic hydrazides were effective.[117] The oxidation of alkylcyanohydrazines to azo-bis nitriles can be carried out with an Oxone/KBr

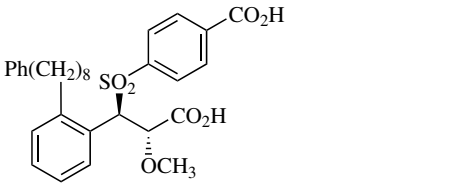
system (eq 67).[118] Nitriles can also be hydrolyzed to amides in moderate to good yields with Oxone/acetone (eq 68).[119]

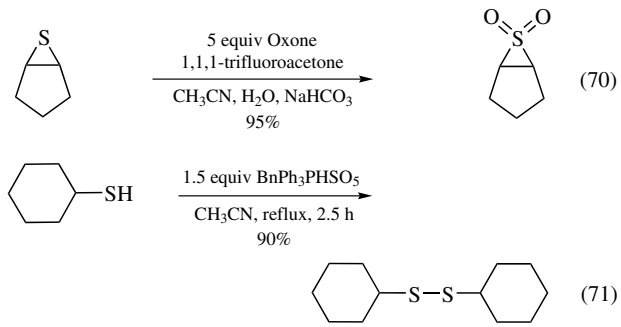


Sulfur Compounds. A convenient procedure for high yielding oxidation of sulfides to either sulfoxides or sulfones using aqueous acetone and Oxone has been reported (eq 69) and has been used to produce SK&F [*107310*] in kilogram quantities.[120] Selectivity is attained by controlling stoichiometry and reaction temperature. These same transformations have also been accomplished with good yield and selectivity on silica gel and alumina. The role of the surfaces has been investigated, and it was found that Oxone is activated by being dispersed on the surface of the adsorbent allowing greater contact with the substrate.[121] Mechanistic studies of sulfide oxidation and thioester hydrolysis by Oxone have also been performed.[122] In addition, oxidation of glycosyl sulfides to glycosyl sulfoxides has been accomplished with Oxone on silica gel.[123]

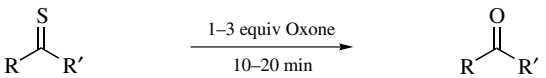


Episulfides can be oxidized to episulfones with Oxone and 1,1,1-trifluoroactetone without considerable episulfoxide formation in many cases (eq 70).[124] Sulfides and thiols can be selectively oxidized to sulfoxides and disulfides, respectively, with the use of $BnPh_3PHSO_5$ in anhydrous aprotic solvents or solvent-free conditions (eq 71).[125,126]



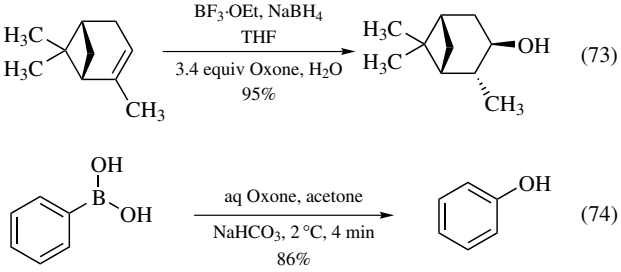


A variety of thiocarbonyl compounds including thioamides, thioureas, and thioesters are converted to their corresponding carbonyl compounds in good yield by simply grinding them with solid Oxone with a mortar and pestle (eq 72).[127] Thioketones remained unchanged under the reaction conditions.



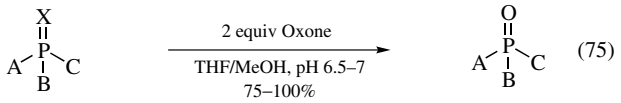
R	R′	Yield (%)
Me	NMePh	95
NH_2	NHPh	85
Ph	OEt	80

Boron, Phosphorus, and Selenium Compounds. Oxone has been used to oxidize carbon-boron bonds during the work-up of hydroboration reactions to obtain high yields of the resultant alcohols (eq 73).[128] Aqueous Oxone/acetone oxidizes electron-poor and electron-rich aromatic and aliphatic boronic acids and esters to the corresponding alcohols rapidly and efficiently (eq 74).[129] A one-pot procedure for the synthesis of *meta*-substituted phenols from benzenes has been developed, and a similar strategy has been devised for the synthesis of Boc-oxindoles from Boc-indoles.[130,131]



Phosphorus(III), phosphothio-, and phosphoseleno- compounds are oxidized by Oxone in THF/MeOH to produce phosphono-, phosphonothio-, and phosphonoseleno- compounds, respectively, with predominant retention of configuration at

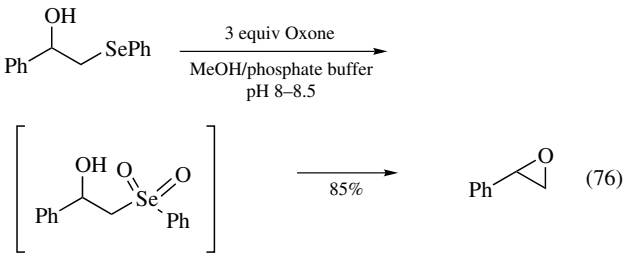
phosphorus (eq 75).[132] Thioalkyl or amino groups attached to phosphorus are unaffected.



(75)

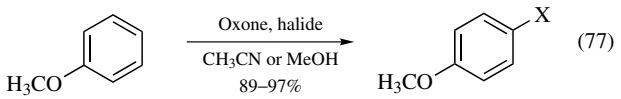
X = lone pair, S, Se
A, B, C, = R, OR, SR, NR_2

Selenides can be oxidized directly to selenones with methanolic buffered Oxone solutions under mild conditions. Selenones can be isolated directly, or if a nucleophile is present, they are displaced giving the substitution product (eq 76).[133] Some α-sulfonyl selenides can be oxidized to selenol esters with Oxone in MeOH or THF.[134]



(76)

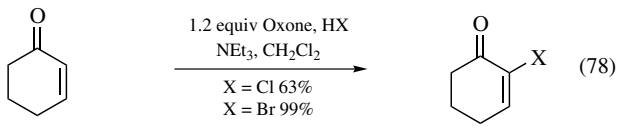
Halides. Oxone oxidizes halides to form electrophilic halogens in situ for a variety of halogenation reactions. Use of in situ generated halogens is advantageous because it obviates the need for storage and handling of dangerous chlorine/bromine and keeps these compounds at low concentrations during reaction. Electron-rich aromatic compounds undergo predominantly *para*-halogenation with Oxone and KX or NH_4I (eq 77).[135–139] Significant amounts of *ortho*-halogenated products are sometimes observed. Phenols can also be iodinated with high yields and selectivity with $BnPh_3PHSO_5$ and KI.[140]



(77)

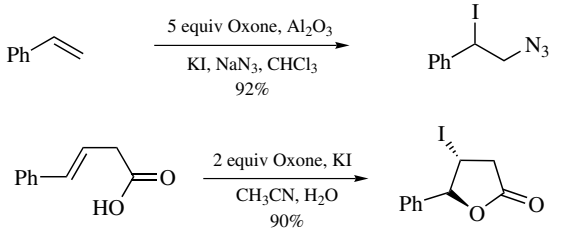
X = Cl, Br, I

Conjugated enones and simple alkenes also undergo halogenation with chlorine or bromine generated from Oxone and the corresponding sodium halide or hydrohalic acid.[141,142] In the case of enones, the addition product can be treated with base to give conjugated vinyl halides (eq 78).



(78)

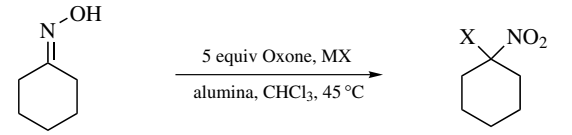
A variety of alkenes undergo azidoiodination with sodium azide, potassium iodide, and Oxone on wet alumina to give azidoiodo compounds regioselectively in high yield (eq 79).[143] These compounds are useful precursors to vinyl azides, amines, and aziridines and are typically synthesized with more expensive and exotic reagents. Similar methods have been used in the iodolactonization and iodoetherification of unsaturated carboxylic acids and alcohols to make five- and six-membered lactones, tetrahydrofurans, and tetrahydropyrans (eq 80).[144]



(79)

(80)

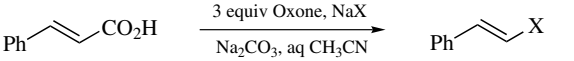
gem-Halo-nitro compounds can be prepared in one step from oximes with Oxone supported on wet basic alumina and NaCl or KBr (eq 81).[145,146] Use of basic alumina is essential in this case due to oxidative deprotection of the oximes to ketones when neutral alumina is used.



(81)

X = Cl 79%
X = Br 81%

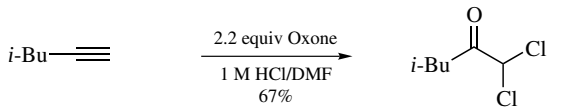
Halodecarboxylation of aromatic α,β-unsaturated carboxylic acids (Hunsdiecker reaction) to make β-halostyrenes has been accomplished with Oxone and sodium halide (eq 82).[147] Bromodecarbonylation and bromodecarboxylation of electron-rich benzaldehydes and benzoic acids has also been observed.[148]



(82)

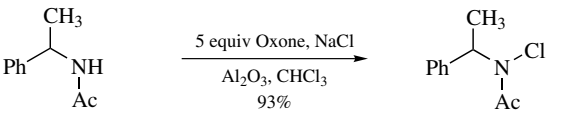
X = Cl 84%
X = Br 88%

Aromatic methyl ketones can be halogenated at the α-position with Oxone and sodium halide, however, competing halogenation of the aromatic ring is significant.[149] α,α-Dichloroketones can be synthesized from alkynes by reaction with Oxone in HCl/DMF (eq 83).[150] Oxone consistently gave better results than MCPBA for this transformation.



(83)

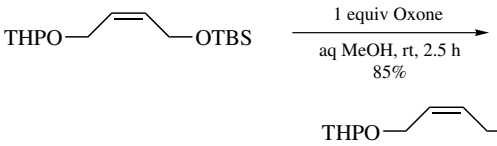
Reaction of amides and carbamates with Oxone on wet alumina and NaCl gives *N*-chlorinated products in high yields (eq 84).[151]



(84)

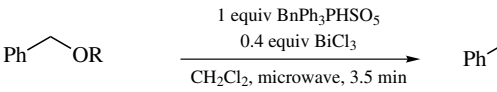
Protecting Group Removal. Several types of alcohol and carbonyl protecting groups can be removed with solutions of Oxone. Deprotection with Oxone offers a mild alternative to traditional methods which often require harshly acidic or basic conditions. Primary alkyl and phenolic TBS ethers are cleaved with aqueous methanolic Oxone (eq 85).[152] Primary alkyl TBS ethers are much more labile and thus can be cleaved in the presence of phenolic TBS ethers by limiting the reaction time. Secondary and tertiary TBS ethers and TBDPS ethers are unaffected. When the reactions

were carried out in the absence of Oxone with solutions of HCl and HF adjusted to the same pH as the Oxone solution, no cleavage was observed for any type of TBS ether after 2.5–3 h, suggesting that Oxone's deprotective ability is not due solely to its acidic nature.



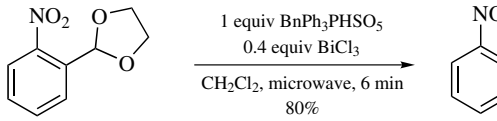
(85)

Oxone in refluxing acetonitrile cleaves TMS and THP ethers to alcohols and acetals to carbonyls.[153] In contrast, $BnPh_3PHSO_5$ has been used to oxidatively cleave TMS and THP ethers and ethylene acetals to carbonyl compounds under microwave irradiation with $BiCl_3$ (eqs 86 and 87).[154] No overoxidation products were observed with this method. Oxone on alumina has also been used to cleave ketals to diols and carbonyl compounds under solvent-free conditions with microwave irradiation.[155]



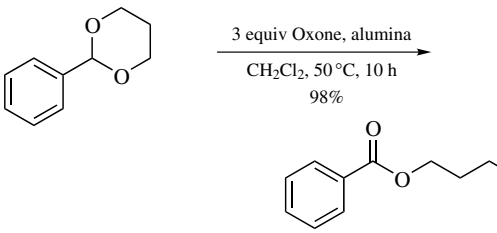
(86)

R = TMS, 90%
R = THP, 90%



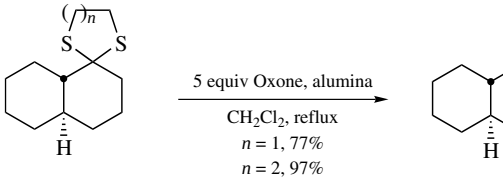
(87)

Cleavage of acetals to esters (eq 88) as well as cleavage of THP ethers with Oxone on wet alumina has also been reported.[156] THP ethers gave mainly the deprotected alcohols along with significant amounts of esterified products.



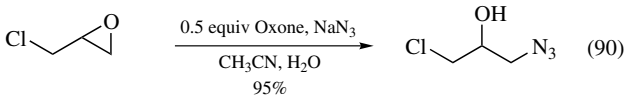
(88)

1,3-Dithiolanes and 1,3-dithianes can also be cleaved by Oxone on wet alumina to give the parent carbonyl compounds in high yields (eq 89).[157] The combination of $BnPh_3PHSO_5$ and $BiCl_3$ has also been applied successfully to the deprotection of 1,3-dithiolanes and 1,3-dithianes under nonaqueous conditions.[158]



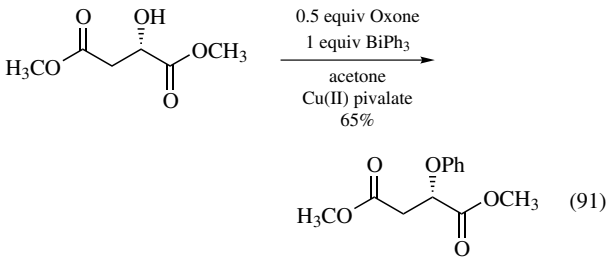
(89)

Miscellaneous. Ring opening of a variety of epoxides and aziridines with NaN_3 in the presence of Oxone in high yields has been accomplished (eq 90).[159] The specific role of Oxone is unclear, however, no ring opening takes place in its absence. It is suggested that the results are due to Oxone's acidic nature.



(90)

Oxone has been used with triarylbismuth and copper salts to effect aryl transfer reactions.[160] Aryl groups can be transferred to alcohols to make phenyl ethers (eq 91). However, two coordination sites on the substrate are necessary.



(91)

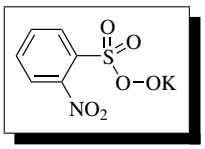
Related Reagents. Dimethyldioxirane; Methyl(trifluoromethyl)dioxirane.

1. Adam, W.; Hadjiarapoglou, L. P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W.; Ed.; Wiley: New York, 1992; Chapter 4, p 195.
2. Curci, R. In *Advances in Oxygenated Processes*; Baumstark A., Ed.; JAI: Greenwich, CT, 1990; Vol. 2; Chapter 1, p 1.
3. Murray, R. W., *Chem. Rev.* **1989**, *89*, 1187.
4. Adam, W.; Edwards, J. O.; Curci, R., *Acc. Chem. Res.* **1989**, *22*, 205.
5. Murray, R. W.; Jeyaraman, R., *J. Org. Chem.* **1985**, *50*, 2847.
6. Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R., *J. Org. Chem.* **1988**, *53*, 3890.
7. Murray, R. W.; Singh, M.; Jeyaraman, R., *J. Am. Chem. Soc.* **1992**, *114*, 1346.
8. Hirano, M.; Oose, M.; Morimoto, T., *Chem. Lett.* **1991**, 331.
9. Hirano, M.; Oose, M.; Morimoto, T., *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1046.
10. Kennedy, R. J.; Stock, A., *J. Org. Chem.* **1960**, *25*, 1901.
11. Bloch, R.; Abecassis, J.; Hassan, D., *J. Org. Chem.* **1985**, *50*, 1544.
12. Zhu, W.; Ford, W. T., *J. Org. Chem.* **1991**, *56*, 7022.
13. Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H., *J. Org. Chem.* **1980**, *45*, 4758.
14. Hofland, A.; Steinberg, H.; De Boer, T. J., *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 350.
15. Corey, P. F.; Ward, F. E., *J. Org. Chem.* **1986**, *51*, 1925.
16. Adam, W.; Hadjiarapoglou, L.; Smerz, A., *Chem. Ber.* **1991**, *124*, 227.
17. Jeyaraman, R.; Murray, R. W., *J. Am. Chem. Soc.* **1984**, *106*, 2462.
18. Mello, R.; Ciminale, F.; Fiorentino, M.; Fusco, C.; Prencipe, T.; Curci, R., *Tetrahedron Lett.* **1990**, *31*, 6097.
19. Hanquet, G.; Lusinchi, X.; Milliet, P., *C.R. Hebd. Seances Acad. Sci., Ser. C* **1991**, *313*, 625.
20. Meunier, B., *Nouv. J. Chim.* **1992**, *16*, 203.
21. De Poorter, B.; Meunier, B., *Nouv. J. Chim.* **1985**, *9*, 393.
22. De Poorter, B.; Ricci, M.; Meunier, B., *Tetrahedron Lett.* **1985**, *26*, 4459.
23. Neumann, R.; Abu-Gnim, C., *J. Chem. Soc., Chem. Commun.* **1989**, 1324.

24. Strukul, G.; Sinigalia, R.; Zanardo, A.; Pinna, F.; Michelin, R., *Inorg. Chem.* **1989**, *28*, 554.
25. Khan, M. M. T.; Chetterjee, D.; Merchant, R. R.; Bhatt, A., *J. Mol. Catal.* **1990**, *63*, 147.
26. Zabrowski, D. L.; Moormann, A. E.; Beck, K. R. J., *Tetrahedron Lett.* **1988**, *29*, 4501.
27. Crandall, J. K.; Reix, T., *J. Org. Chem.* **1992**, *57*, 6759.
28. Itahara, T., *Chem. Lett.* **1991**, 1591.
29. Kettani, A. E.; Bernadou, J.; Meunier, B., *J. Org. Chem.* **1989**, *54*, 3213.
30. Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T., *J. Org. Chem.* **1988**, *53*, 2087.
31. Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, R. T.; Chen, B. C., *J. Org. Chem.* **1992**, *57*, 7274.
32. Hajipour, A. R.; Pyne, S. G., *J. Chem. Res. (S)* **1992**, 388.
33. Kim, J. N.; Ryu, E. K., *J. Org. Chem.* **1992**, *57*, 6649.
34. Trost, B. M.; Curran, D. P., *Tetrahedron Lett.* **1981**, *22*, 1287.
35. Hirano, M.; Tomaru, J.; Morimoto, T., *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3752.
36. Evans, T. L.; Grade, M. M., *Synth. Commun.* **1986**, *16*, 1207.
37. Greenhalgh, R. P., *Synlett* **1992**, 235.
38. Davis, F. A.; Lal, S. G.; Durst, H. D., *J. Org. Chem.* **1988**, *53*, 5004.
39. Quallich, G. J.; Lackey, J. W., *Tetrahedron Lett.* **1990**, *31*, 3685.
40. Colonna, S.; Gaggero, N.; Leone, M.; Pasta, P., *Tetrahedron* **1991**, *47*, 8385.
41. Reddey, R. N., *Synth. Commun.* **1987**, *17*, 1129.
42. Tabuchi, T.; Nojima, M.; Kusabayashi, S., *J. Chem. Soc., Perkin Trans. 1* **1991**, 3043.
43. Travis, B. R.; Ciaramitaro, B. P.; Borhan, B., *Eur. J. Org. Chem.* **2002**, 3429.
44. Trost, B. M.; Braslau, R., *J. Org. Chem.* **1988**, *53*, 532.
45. Campestrini, S.; Di Furia, F.; Labat, G.; Novello, F., *J. Chem. Soc., Perkin Trans. 2* **1994**, 2175.
46. Page, P. C. B.; Barros, D.; Buckley, B. R.; Ardakani, A.; Marples, B. A., *J. Org. Chem.* **2004**, *69*, 3595.
47. Hajipour, A. R.; Mallakpour, S. E.; Adibi, H., *Chem. Lett.* **2000**, 460.
48. Yan, J.; Travis, B. R.; Borhan, B., *J. Org. Chem.* **2004**, *69*, 9299.
49. Ashford, S. W.; Grega, K. C., *J. Org. Chem.* **2001**, *66*, 1523.
50. Ballini, R.; Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O., *Synlett* **1998**, 1049.
51. Webb, K. S.; Ruszkay, J. S., *Tetrahedron* **1998**, *54*, 401.
52. Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B., *Org. Lett.* **2003**, *5*, 1031.
53. Bose, D. S.; Narsaiah, A. V., *Tetrahedron Lett.* **1998**, *39*, 6533.
54. Bagherzadeh, M., *Tetrahedron Lett.* **2003**, *44*, 8943.
55. Bolm, C.; Magnus, A. S.; Hildebrand, J. P., *Org. Lett.* **2000**, *2*, 1173.
56. Koo, B.-S.; Lee, C. K.; Lee, K.-J., *Synth. Commun.* **2002**, *32*, 2115.
57. Hajipour, A. R.; Mallakpour, S.; Adibi, H., *Chem. Lett.* **2000**, 460.
58. Denmark, S. E.; Wu, Z., *Synlett* **1999**, 847.
59. Frohn, M.; Shi, Y., *Synthesis* **2000**, 1979.
60. Shi, Y., *Acc. Chem. Res.* **2004**, *37*, 488.
61. Yang, D., *Acc. Chem. Res.* **2004**, *37*, 497.
62. Curci, R.; Fiorentino, M.; Serio, M. R., *J. Chem. Soc., Chem. Commun.* **1984**, 155.
63. Yang, D.; Tang, Y.-C.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K., *J. Am. Chem. Soc.* **1996**, *118*, 491.
64. Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W., *J. Am. Chem. Soc.* **1996**, *118*, 11311.
65. Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K., *J. Am. Chem. Soc.* **1998**, *120*, 5943.
66. Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H., *J. Org. Chem.* **1997**, *62*, 8288.
67. Denmark, S. E.; Matsuhashi, H., *J. Org. Chem.* **2002**, *67*, 3479.
68. Stearman, C. J.; Behar, V., *Tetrahedron Lett.* **2002**, *43*,1943.
69. Denmark, S. E.; Forbes, D. C.; Hays, D. S.; De Pue, J. S.; Wilde, R. G., *J. Org. Chem.* **1995**, *60*, 1391.
70. Tu, Y.; Wang, Z.-X.; Shi, Y., *J. Am. Chem. Soc.* **1996**, *118*, 9806.
71. Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y., *J. Am. Chem. Soc.* **1997**, *119*, 11224.
72. Shu, L.; Shi, Y., *Tetrahedron Lett.* **2004**, *45*, 8115.
73. Aggarwal, V. K.; Wang, M. F., *J. Chem. Soc., Chem. Commun.* **1996**, 191.
74. Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B., *J. Org. Chem.* **1998**, *63*, 2774.
75. Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M., *Synlett* **2000**, *12*, 1810.
76. Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D., *Org. Lett.* **2001**, *16*, 2587.
77. Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S., *Tetrahedron* **1999**, *55*, 2341.
78. Page, P. C. B.; Buckley, B. R.; Blackler, A. J., *Org. Lett.* **2004**, *6*, 1543.
79. Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blackler, A. J., *Org. Lett.* **2005**, *7*, 375.
80. Armstrong, A., *Angew. Chem. Int. Ed.* **2004**, *43*, 1460.
81. Aggarwal, V. K.; Lopin, C.; Sandrinelli, F., *J. Am. Chem. Soc.* **2003**, *125*, 7596.
82. Ho, C.-Y.; Chen, Y.-C.; Wong, M.-K.; Yang, D., *J. Org. Chem.* **2005**, *70*, 898.
83. Travis, B. R.; Narayan, R. S.; Borhan, B., *J. Am. Chem. Soc.* **2002**, *124*, 3824.
84. Schomaker, J. M.; Travis, B. R.; Borhan, B., *Org. Lett.* **2003**, *5*, 3089.
85. Travis, B.; Borhan, B., *Tetrahedron Lett.* **2001**, *42*, 7741.
86. Yang, D.; Zhang, C., *J. Org. Chem.* **2001**, *66*, 4814.
87. Plietker, B., *J. Org. Chem.* **2003**, *68*, 7123.
88. Plietker, B., *J. Org. Chem.* **2004**, *69*, 8287.
89. Plietker, B., *Org. Lett.* **2004**, *6*, 289.
90. Rani, S.; Vankar, Y. D., *Tetrahedron Lett.* **2003**, *44*, 907.
91. Yang, D.; Chen, F.; Dong, Z.-M.; Zhang, D.-W., *J. Org. Chem.* **2004**, *69*, 2221.
92. Yang, D.; Wong, M.-K.; Wang, X.-C.; Tang, Y.-C., *J. Am. Chem. Soc.* **1998**, *120*, 6611.
93. Wong, M.-K.; Chung, N.-W.; He, L.; Wang, X.-C.; Yan, Z.; Tang, Y-C.; Yang, D., *J. Org. Chem.* **2003**, *68*, 6321.
94. Adam, W.; SahaMoller, C. R.; Zhao, C.-G., *Tetrahedron: Asymmetry* **1998**, *9*, 4117.
95. Adam, W.; Saha-Moller, C. R.; Zhao, C.-G., *J. Org. Chem.* **1999**, *64*, 7492.
96. Cammarota, L.; Campestrini, S.; Carrieri, M.; Di Furia, F.; Ghiotti, P., *J. Mol. Catal. A* **1999**, *137*, 155.
97. Webb, K. S.; Seneviratne, V., *Tetrahedron Lett.* **1995**, *36*, 2377.
98. Noecker, L.; Giuliano, R. M.; Cooney, M.; Boyko, W.; Zajac, Jr., W. W., *J. Carbohydr. Chem.* **2002**, *21*, 539.
99. Fields, J. D.; Kropp, P. J., *J. Org. Chem.* **2000**, *65*, 5937.
100. Brik, M. E., *Tetrahedron Lett.* **1995**, *36*, 5519.
101. Zolfigol, M. A.; Bagherzadeh, M.; Choghamarani, A. G.; Keypour, H.; Salehzadeh, S., *Synth. Commun.* **2001**, *31*, 1161.
102. Zolfigol, M. A.; Bagherzadeh, M.; Madrakian, E.; Ghaemi, E.; Taquian-Nasab, A., *J. Chem. Res. (S).* **2001**, 140.
103. Priewisch, B.; Rück-Braun, K., *J. Org. Chem.* **2005**, *70*, 2350.
104. Bose, D. S.; Vanajatha, G., *Synth.Commun.* **1998**, *28*, 4531.
105. Bose, D. S.; Srinivas, P., *Synth. Commun.* **1997**, *27*, 3835.
106. Bose, D. S.; Narsaiah, A. V.; Lakshminarayana, V., *Synth. Commun.* **2000**, *30*, 3121.

107. Bigdeli, M. A.; Nikje, M. M. A.; Heravi, M. M., *Phosphorus, Sulfur, Silicon* **2002**, *177*, 15.
108. Paradkar, V. M.; Latham, T. B.; Demko, D. M., *Synlett* **1993**, 1059.
109. Kim, J. N.; Jung, K. S.; Lee, H. J.; Son, J. S., *Tetrahedron Lett.* **1997**, *38*, 1597.
110. Curini, M.; Rosati, O.; Pisani, E., *Tetrahedron Lett.* **1997**, *38*, 1239.
111. Jung, J. C.; Kim, K. S.; Kim, Y. H., *Synth. Commun.* **1992**, *22*, 1583.
112. Hajipour, A. R.; Mallakpour, S. E.; Baltork, I. M.; Adibi, H., *Synth. Commun.* **2001**, *31*, 3401.
113. Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O., *Synth. Commun.* **1998**, *28*, 3057.
114. Beaulieu, P. L.; Haché, B.; von Moos, E., *Synthesis* **2003**, 1683.
115. Zolfigol, M. A.; Bagherzadeh, M.; Chehardoli, G.; Mallakpour, S. E., *Synth. Commun.* **2001**, *31*, 1149.
116. Mohajer, D.; Iranpoor, N.; Rezaeifard, A., *Tetrahedron Lett.* **2004**, *45*, 631.
117. Kulkarni, P. P.; Kadam, A. J.; Desai, U. V.; Mane, R. B.; Wadgaonkar, P. P., *J. Chem. Res. (S)* **2000**, 184.
118. Tamhankar, B. V.; Desai, U. V.; Mane, R. B.; Kulkarni, P. P.; Wadgaonkar, P. P., *Synth. Commun.* **2002**, *32*, 3643.
119. Bose, D. S.; Baquer, S. M., *Synth. Commun.* **1997**, *27*, 3119.
120. Webb, K. S., *Tetrahedron Lett.* **1994**, *35*, 3457.
121. Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R., *J. Am. Chem. Soc.* **2000**, *122*, 4280.
122. Bunton, C. A.; Foroudian, H. J.; Kumar, A., *J. Chem. Soc., Perkin Trans. 2* **1995**, 33.
123. Chen, M.-Y.; Patkar, L. N.; Chen, H.-T.; Lin, C.-C., *Carbohydr. Res.* **2003**, *338*, 1327.
124. Johnson, P.; Taylor, R. J. K., *Tetrahedron Lett.* **1997**, *38*, 5873.
125. Hajipour, A. R.; Mallakpour, S. E.; Adibi, H., *J. Org. Chem.* **2002**, *67*, 8666.
126. Hajipour, A. R.; Mallakpour, S. E.; Adibi, H., *Phosphorus, Sulfur, Silicon* **2002**, *177*, 2277.
127. Baltork, I. M.; Sadeghi, M. M.; Esmayilpour, K., *Synth. Commun.* **2003**, *33*, 953.
128. Ripin, D. H. B.; Cai, W.; Brenek, S. J., *Tetrahedron Lett.* **2000**, *41*, 5817.
129. Webb, K. S.; Levy, D., *Tetrahedron Lett.* **1995**, *36*, 5117.
130. Maleczka, R. E.; Jr., Shi, F.; Holmes, D.; Smith, M. R., III, *J. Am. Chem. Soc.* **2003**, *125*, 7792.
131. Vazquez, E.; Payack, J. F., *Tetrahedron Lett.* **2004**, *45*, 6549.
132. Woźniak, L. A.; Stec, W. J., *Tetrahedron Lett.* **1999**, *40*, 2637.
133. Ceccherelli, P.; Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O., *J. Org. Chem.* **1995**, *60*, 8412.
134. Yi, J. S.; Kim, K., *J. Chem. Soc., Perkin Trans. 1* **1999**, 71.
135. Tamhankar, B. V.; Desai, U. V.; Mane, R. B.; Wadgaonkar, P. P.; Bedekar, A. V., *Synth. Commun.* **2001**, *31*, 2021.
136. Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V., *Synth. Commun.* **2002**, *32*, 279.
137. Narender, N.; Srinivasu, P.; Prasad, M. R.; Kulkarni, S. J.; Raghavan, K. V., *Synth. Commun.* **2002**, *32*, 2313.
138. Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V., *Synth. Commun.* **2002**, *32*, 2319.
139. Mohan, K. V. V. K.; Narender, N.; Kulkarni, S. J., *Tetrahedron Lett.* **2004**, *45*, 8015.
140. Hajipour, A. R.; Adibi, H., *J. Chem. Res.* **2004**, 294.
141. Dieter, R. K.; Nice, L. E.; Velu, S. E., *Tetrahedron Lett.* **1996**, *37*, 2377.
142. Kim, K.-M.; Park, I.-H., *Synthesis* **2004**, 2641.
143. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O., *Tetrahedron Lett.* **2002**, *43*, 1201.
144. Curini, M.; Epifano, F.; Marcotullio, M. C.; Montanari, F., *Synlett* **2004**, 368.
145. Ceccherelli, P.; Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O., *Tetrahedron Lett.* **1998**, *39*, 4385.
146. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Rossi, M., *Tetrahedron* **1999**, *55*, 6211.
147. You, H.-W.; Lee, K.-J., *Synlett* **2001**, 105.
148. Koo, B.-S.; Kim, E.-H.; Lee, K.-J., *Synth. Commun.* **2002**, *32*, 2275.
149. Kim, E.-H.; Koo, B.-S.; Song, C. E.; Lee, K. J., *Synth. Commun.* **2001**, *31*, 3627.
150. Kim, K. K.; Kim, J. N.; Kim, K. M.; Kim, H. R.; Ryu, E. K., *Chem. Lett.* **1992**, 603.
151. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Tsadjout, A., *Synlett* **2000**, 813.
152. Sabitha, G.; Syamala, M.; Yadav, J. S., *Org. Lett.* **1999**, *1*, 1701.
153. Baltork, I. M.; Amini, M. K.; Farshidipoor, S., *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2775.
154. Hajipour, A. R.; Mallakpour, S. E.; Baltork, I. M.; Adibi, H., *Synth. Commun.* **2001**, *31*, 1625.
155. Bose, D. S.; Jayalakshmi, B.; Narsaiah, A. V., *Synthesis* **2000**, 67.
156. Curini, M.; Epifano,F.; Marcotullio, M. C.; Rosati, O., *Synlett* **1999**, 777.
157. Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O., *Synlett* **1996**, 767.
158. Hajipour, A. R.; Mallakpour, S. E.; Baltork, I. M.; Adibi, H., *Phosphorus, Sulfur, Silicon* **2002**, *177*, 2805.
159. Sabitha, G.; Babu, R. S.; Reddy, M. S. K.; Yadav, J. S., *Synthesis* **2002**, 2254.
160. Sheppard, G. S., *Synlett* **2002**, 1207.

Potassium *o*-Nitrobenzeneperoxysulfonate



[–] $C_6H_4KNO_6S$ (MW 257.28)

InChI = 1/C6H5NO6S.K/c8-7(9)5-3-1-2-4-6(5)14(11,12)13-10;/h1-4,10H;/q;+1/p-1/fC6H4NO6S.K/h10h;/q-1;m

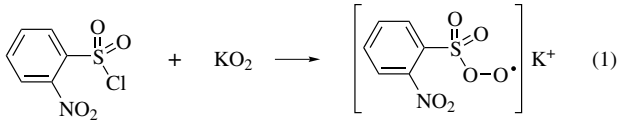
InChIKey = UQHRYKBMJVIFDE-OAEQBNDPCA

(epoxidizes alkenes[1] and arenes;[2] oxidizes aryl methylenes,[3] thiocarbonyl compounds,[4] and sulfoxides[5])

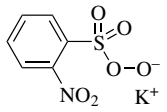
Solubility: sol MeCN, DMF.

Form Supplied in: not commercially available.

Preparative Methods: reactive intermediate (**1**) is generated in situ according to eq 1. Many experiments suggest that the reactive intermediate formed by mixing (**3**) and (**4**) is a radical;[6] however, the existence of the anion (**2**) cannot be ruled out.



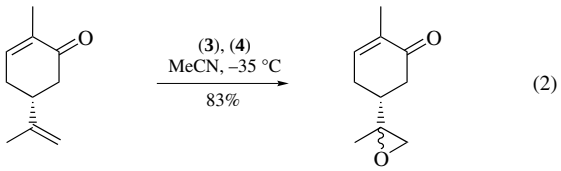
(3) **(4)** **(1)** (1)



(**2**)

Handling, Storage, and Precautions: intermediate (**1**) cannot be stored, but is generated and reacted in situ. Reactions are carried out under dry argon atmosphere.

Epoxidation of Alkenes. Alkenes are epoxidized under mild conditions in high yields by the peroxy intermediate (**1**); for example, see the preparation of epoxide (**6**) from (−)-carvone (**5**) (eq 2).

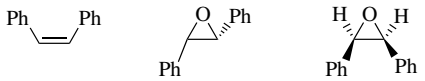


(2)

(**5**) (**6**)

A solution of sulfonyl chloride (**3**) (0.22 g, 1.0 mmol) and (−)-carvone (**5**) (0.09 g, 0.6 mmol; MeCN, 2.0 mL) is added to a heterogeneous solution of KO_2 (0.222 g; 3.0 mmol, MeCN, 1.0 mL) at −35 °C under dry argon atmosphere. After stirring at −35 °C for 4 h, the reaction mixture is concentrated and then extracted with $CHCl_3$. The residue obtained after removal of solvent is purified by preparative TLC to furnish (**6**) in 83% yield.[1]

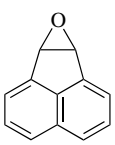
Epoxidation of *cis*-stilbene (**7**) by reaction with the intermediate (**1**) furnishes a 70:30 mixture of oxides (**8**) and (**9**); this reaction suggests that the reactive intermediate is a radical.[2]



(**7**) (**8**) (**9**)

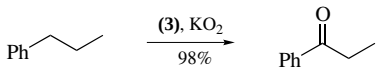
Metal peroxides have low solubility in organic solvents and are usually used in the presence of crown ethers. KO_2 is soluble enough in aprotic solvents such as MeCN and DMF; hence there is no need to use crown ether for preparing the intermediate according to eq 1.[2]

Epoxidation of Arenes. Certain arenes (acenaphthylene, phenanthrene, and pyrene) are readily oxidized to the corresponding arene oxides by the peroxy intermediate (**1**) generated from sulfonyl chloride (**3**) in polar aprotic solvents such as MeCN and DMF. Superoxide (**4**) is a strong base and reactions with (**1**) take place under mild and basic conditions. Acenaphthylene oxide (**10**) is unstable under acidic conditions but is more stable under basic conditions. Oxide (**10**) was obtained in 95% yield.[2]



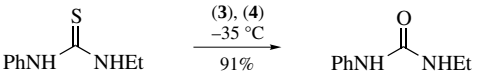
(**10**)

Oxidation of Benzylic Methylene Compounds. The peroxy intermediate (**1**) generated from sulfonyl chloride (**3**) oxidized compounds containing benzylic methylene groups to ketones under mild conditions (−35 °C) (eq 3).[3]



(3)

Oxidative Desulfurization of Thiocarbonyl Compounds. Thiocarbonyl compounds such as substituted thioureas, thioamides, and thiocarbamates undergo oxidative desulfurization in high yields when reacted with the peroxy intermediate (**1**) under mild conditions (eq 4).[4]



(4)

Oxidation of Sulfoxides. Dialkyl, alkyl aryl, and diaryl sulfoxides are readily oxidized to sulfones in excellent yields under mild conditions (−30 °C) in MeCN by the peroxy intermediate (**1**). Oxidation of the unsaturated sulfoxide (**11**) was chemoselective; it furnished the sulfone (**12**) in 70% yield when reacted with (**1**) for 5 h. The double bond was not epoxidized.[5] Similar chemoselective epoxidation has been carried out with only one other reagent (potassium hydrogen persulfate).[7]

(**11**) (**12**)

The peroxy intermediate (**1**) is an excellent reagent for the synthesis of acid-sensitive benzylic epoxides from alkenes, the oxidation of benzylic CH_2 to C=O, and the chemoselective oxidation of alkene sulfoxides to alkene sulfones. It is noteworthy that the reactions are carried out under mild conditions (−35 °C).

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1. Kim, Y. H.; Chung, B. C., *J. Org. Chem.* **1983**, *48*, 1562.
2. Lee, H. K.; Kim, K. S.; Kim, J. C.; Kim, Y. H., *Chem. Lett.* **1988**, 561.
3. Kim, Y. H.; Kim, K. S.; Lee, H. K., *Tetrahedron Lett.* **1989**, *30*, 6357.
4. Kim, Y. H.; Chung, B. C.; Chang, H. S., *Tetrahedron Lett.* **1985**, *26*, 1079.
5. Kim, Y. H.; Lee, H. K., *Chem. Lett.* **1987**, 1499.
6. Kim, Y. H.; Lim, S. C.; Hoshino, M.; Ohtsuka, Y.; Ohishi, T., *Chem. Lett.* **1989**, 167.
7. Trost, B. M.; Curran, D. P., *Tetrahedron Lett.* **1981**, *22*, 1287.

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Potassium Nitrosodisulfonate[1]

$(KSO_3)_2NO$

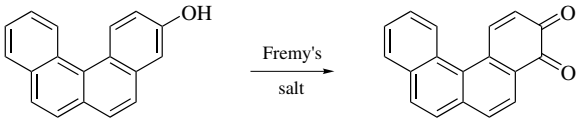
[14293-70-0] $K_2NO_7S_2$ (MW 268.35)
InChI = 1/2K.H2NO7S2/c;;2-1(9(3,4)5)10(6,7)8/h;;(H,3,4,5)
(H,6,7,8)/q2*+1;/p-2/f2K.NO7S2/q2m;-2
InChIKey = IHSLHAZEJBXKMN-URMPCEJXCL

(oxidizing reagent for synthesis of quinones from phenols,[2] naphthols,[9] and anilines;[18] oxidant for conversion of benzylic alcohols to aldehydes or ketones[30] and amino acids to α-keto acids;[31] preparation of heterocyclic quinones;[20–22] oxidative aromatization[29])

Alternate Name: Fremy's salt.
Solubility: sol H_2O.
Form Supplied in: orange powder; widely available.
Preparative Methods: see Zimmer et al.[1]
Handling, Storage, and Precautions: in solid form, this reagent is rather unstable. It sometimes undergoes spontaneous decomposition which occasionally results in a violent explosion attributed to impurities such as chloride ion, manganese dioxide, or nitrite ion. Stored in a desiccator over calcium oxide in the presence of ammonium carbonate to provide an ammoniacal atmosphere, it is stable for several months.

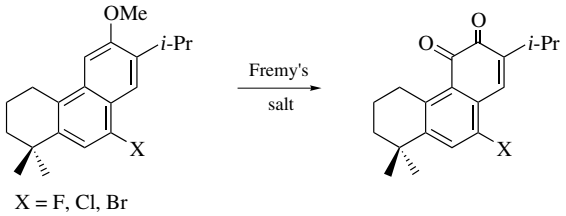
Phenol Oxidations. This reagent oxidizes phenols to the corresponding 1,2- or 1,4-quinones under mild conditions and usually in good yield. The substituents on the aromatic ring control the ratio of *ortho*- and *para*-quinones.[2] *para*-Unsubstituted phenols bearing a variety of substituents in the *ortho* and *meta* positions (e.g. alkyl,[3,4] alkyloxy and/or bromine,[5] crown ether substituents,[6] and *p*-hydroxybenzylamines and primary *p*-hydroxybenzamides[7]) are generally converted to 1,4-quinones. Phenols with easy-to-displace *para* substituents, such as CH_2OH, Br, Cl, CO_2H, $CONH_2$, and CH(OH)CN, undergo oxidation to form 1,4-quinones. 1,2-Quinones are formed if the *para* substituents are alkoxy, alkyl, or aryl.[8] See also lead(IV) oxide and salcomine.

Naphthol Oxidations. α-Naphthols can be oxidized to 1,2- or 1,4-naphthoquinones by Fremy's salt.[9] Again, the nature of the *para* substituent is critical. 1,4-Naphthoquinones predominate if the *para* position is unsubstituted.[10] 1,2-Naphthoquinones are formed if an alkyl or aryl group occupies the *para* position,[9] if there is a hydroxy group in the 2-position,[9] or if the *para* position is hindered.[11] Approximately equal amounts of 1,2- and 1,4-naphthoquinones are obtained if a hydroxy group occupies the 5-position.[9] It has been reported that 1,4-naphthoquinones are produced from oxidation of 2- or 9-SMe substituted phenols.[12] β-Naphthols are generally oxidized to 1,2-naphthoquinones (eq 1).[13]



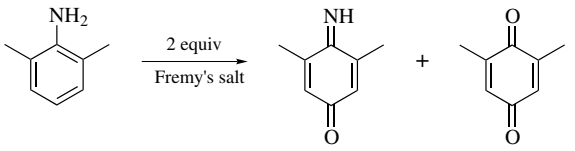
(1)

The methyl ether of a β-naphthol has been reported to afford a 1,2-quinone (eq 2).[14]



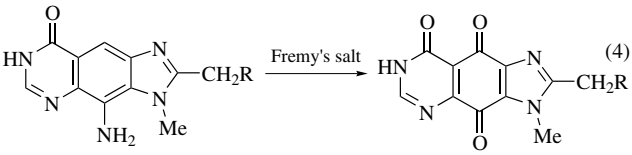
X = F, Cl, Br
(2)

Aniline Oxidations. 1,4-Quinones are formed by the reaction of 2,6-disubstituted and 2,3,6-trisubstituted anilines and Fremy's salt.[15] Other *ortho* or *meta* methoxy-substituted aromatic amines were converted to the corresponding 1,4-quinones[16] and 1,2-quinones.[17] In one case the oxidation intermediate, a quinone imine which subsequently undergoes hydrolysis to the quinone, has been isolated (eq 3).[18]



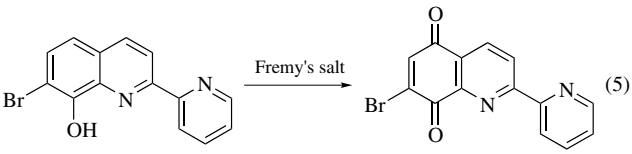
(3)

Hypoxanthine analogs were formed by Fremy's salt oxidation (eq 4).[19]



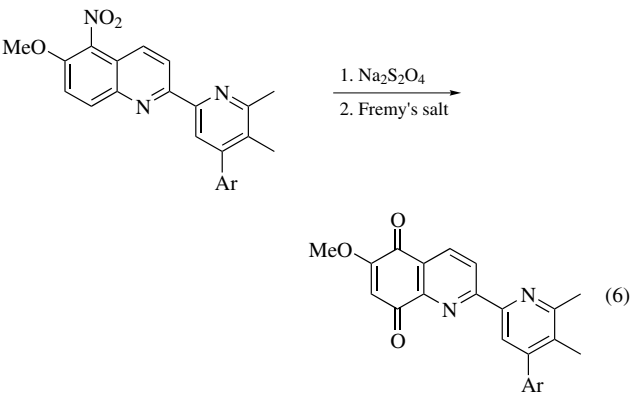
R = H, OMe
(4)

Oxidations to Quinoline Quinones. Quinolinols are converted to quinoline quinones (eq 5).[20]



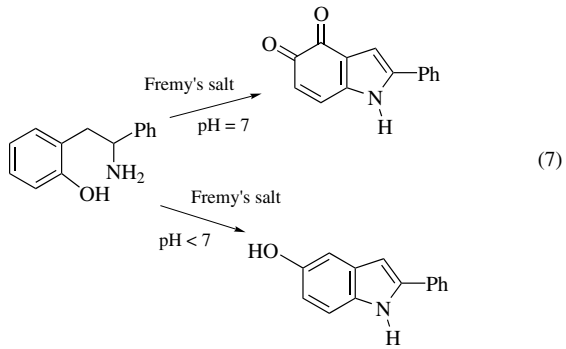
(5)

In an approach to streptonigrin, Fremy's salt was utilized to oxidize a methoxy aniline by a phase-transfer procedure (eq 6).[21]

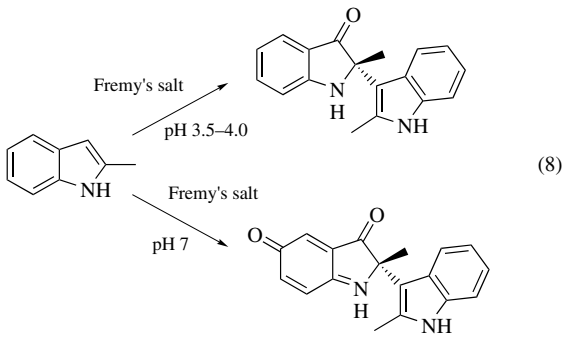


(6)

Oxidations to Indole Derivatives. The derivatives of *ortho*-hydroxy phenethylamine were converted into indoles (eq 7).[22] Presumably the primary oxidation product is protected from secondary oxidation by protonation at lower pH. Likewise, in solution at different pH, 2-methylindole dimerizes to different products (eq 8).[23]

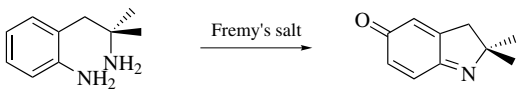


(7)



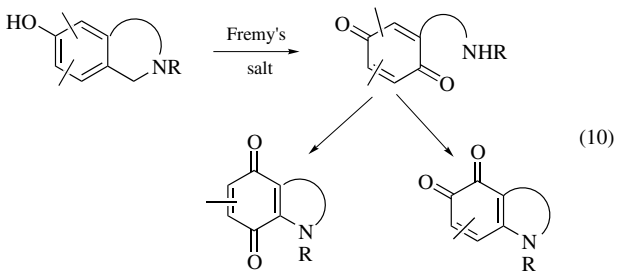
(8)

The derivatives of *ortho*-aminophenethylamine were converted to indoline 1,4-quinone imides (eq 9).[24] No oxidation at the 3-position or 4-position was observed if the α-position was occupied by two alkyl groups.



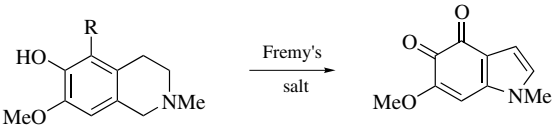
(9)

A novel route to heterocyclic quinones, based on Fremy's salt promoted oxidation, has been developed recently (eq 10).[25]



(10)

With this methodology, isoquinoline derivatives were converted with ring contraction to the 1,2-quinone indoles in a buffered (pH 6.1) two-phase (CH_2Cl_2–H_2O) system (eq 11).

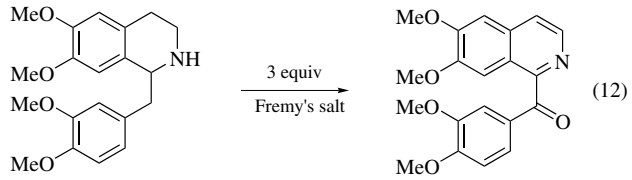


R = H or OMe

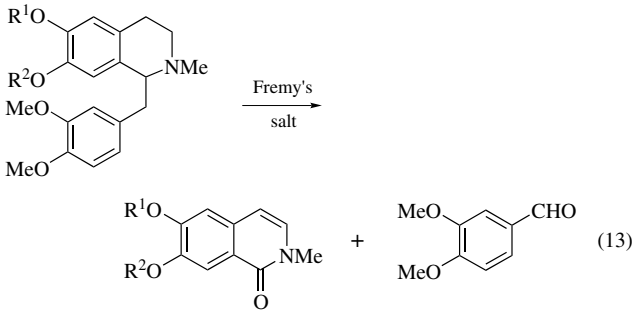
(11)

5-Hydroxybenzofuran is oxidized to the 4,5-*ortho*-quinone.[26] Bisquinones[27] and other heterocyclic quinones[28] were prepared by Fremy's salt oxidation.

Tetrahydroisoquinoline Oxidation. Papaveraldine could be produced by Fremy's salt oxidation over 7 days in 30% yield (eq 12). The corresponding *N*-alkyl tetrahydroisoquinolines give cleavage products (eq 13).[29]



(12)

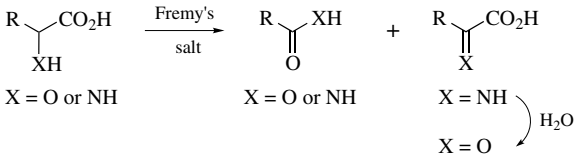


(a) $R^1 = R^2 = Me$; (b) $R^1 + R^2 = CH_2$

(13)

Other Reactions. Benzylic alcohols could be selectively oxidized to aldehydes or ketones in the presence of allylic alcohols and saturated alcohols by Fremy's salt in a phase-transfer system.[30]

Some α-amino and α-hydroxy acids were oxidized to the corresponding α-keto acids (dehydrogenation) and/or to the acids or amides (with decarboxylation) (eq 14).[31]



(14)

1. Zimmer, H.; Lankin, D. C.; Horgan, S. W., *Chem. Rev.* **1971**, *71*, 229.
2. Deya, P. M.; Dopico, M.; Raso, A. G.; Morey, J.; Saa, J. M., *Tetrahedron* **1987**, *43*, 3523.
3. Teuber, H.-J.; Thaler, G., *Chem. Ber.* **1959**, *92*, 667.
4. (a) Magnusson, R., *Acta Chem. Scand.* **1966**, *18*, 759. (b) Engler, T. A.; Sampath, U.; Naganathan, S.; Velde, D. V.; Takusagawa, F.; Yohannes, D., *J. Org. Chem.* **1989**, *54*, 5712.
5. (a) Saa, J. M.; Llobera, A.; Garcia-Raso, A.; Costa, A.; Deya, P. M., *J. Org. Chem.* **1988**, *53*, 4263. (b) Singh, S. B.; Pettit, G. R., *J. Org. Chem.* **1989**, *54*, 4105.
6. (a) Chapoteau, E.; Czech, B. P.; Kumar, A.; Pose, A., *J. Org. Chem.* **1989**, *54*, 861. (b) Hayakawa, K.; Kido, K.; Kanematsu, K., *J. Chem. Soc., Perkin Trans. 1* **1988**, 511.
7. Saa, J. M.; Llobera, A.; Deya, P. M., *Chem. Lett.* **1987**, 771.
8. Begley, M. J.; Fish, P. V.; Pattenden, G.; Hodgson, S. T., *J. Chem. Soc., Perkin Trans. 1* **1990**, 2263.

9. Teuber, H.-J.; Gotz, N., *Chem. Ber.* **1954**, 87, 1236. Teuber, H.-J.; Lindner, H., *Chem. Ber.* **1959**, *92*, 921 and 927.
10. Ashnagar, A.; Bruce, J. M.; Lloyd-Williams, P., *J. Chem. Soc., Perkin Trans. 1* **1988**, 559.
11. (a) Ciufolini, M. A.; Byrne, N. E., *J. Am. Chem. Soc.* **1991**, *113*, 8016. (b) Ciufolini, M. A.; Byrne, N. E., *Tetrahedron Lett.* **1989**, *30*, 5559.
12. Coll, G.; Morey, J.; Costa, A.; Saa, J. M., *J. Org. Chem.* **1988**, *53*, 5345.
13. (a) Pataki, J.; Raddo, P. D.; Harvey, R. G., *J. Org. Chem.* **1989**, *54*, 840. (b) Ray, J. K.; Kar, G. K.; Karmakar, A. C., *J. Org. Chem.* **1991**, *56*, 2268. (c) Ramesh, D.; Kar, G. K.; Chatterjee, B. G.; Ray, J. K., *J. Org. Chem.* **1988**, *53*, 212. (d) Sharma, P. K., *Synth. Commun.* **1993**, *23*, 389. (e) Chang, H. M.; Chui, K. Y.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P. Lee, C. M.; Sham, H. L.; Wong, H. N. C., *J. Med. Chem.* **1991**, *34*, 1675.
14. He, Y.; Chang, H. M.; Lau, Y. K.; Cui, Y. X.; Wang, R. J.; Mak, T. C. W.; Wong, H. N. C.; Lee, C. M., *J. Chem. Soc., Perkin Trans. 1* **1990**, 3359.
15. Teuber, H. J.; Hasselbach, M., *Chem. Ber.* **1959**, *92*, 674.
16. (a) Helissey, P.; Giorgi-Renault, S.; Renault, J.; Cros, S., *Chem. Pharm. Bull.* **1989**, *37*, 675. (b) Kende, A. S.; Ebert, F. H.; Battista, R.; Boatman, R. J.; Lorah, D. P.; Lodge, E., *Heterocycles* **1984**, *21*, 91. (c) Brown, P. E.; Lewis, R. A.; Waring, M. A., *J. Chem. Soc., Perkin Trans. 1* **1990**, 2979.
17. Cambie, R. C.; Grimsdale, A. C.; Rutledge, P. S.; Woodgate, P. D., *Aust. J. Chem.* **1990**, *43*, 485.
18. Horner, L.; Sturm, K., *Chem. Ber.* **1955**, *88*, 329.
19. (a) Lee, C. H.; Gilchrist, J. H.; Skibo, E. B., *J. Org. Chem.* **1986**, *51*, 4784. (b) Dempcy, R. O.; Skibo, E. B., *J. Org. Chem.* **1991**, *56*, 776.
20. (a) Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C., *J. Med. Chem.* **1987**, *30*, 1918. (b) Saito, H.; Hirata, T.; Kasai, M.; Fujimoto, K.; Ashizawa, T.; Morimoto, M.; Sato, A., *J. Med. Chem.* **1991**, *34*, 1959. (c) Kozikowski, A P.; Sugiyama, K.; Springer, J. P., *J. Org. Chem.* **1981**, *46*, 2426. (d) see Ref. 11.
21. (a) Kende, A. S.; Ebert, F. H.; Battista, R.; Boatman, R. J.; Lorah, D. P.; Lodge, E., *Heterocycles* **1984**, *21*, 91. (b) Kende, A. S.; Ebetino, F. H., *Tetrahedron Lett.* **1984**, *25*, 923.
22. Teuber, H.-J.; Glosauer, O., *Chem. Ber.* **1965**, *98*, 2648.
23. Teuber, H.-J.; Staiger, G., *Chem. Ber.* **1955**, *88*, 1066.
24. Teuber, H.-J.; Glosauer, O., *Chem. Ber.* **1965**, *98*, 2939.
25. Saa, J. M.; Capo, M.; Marti, C.; Garcia-Raso, A., *J. Org. Chem.* **1990**, *55*, 288.
26. Lee, J.; Tang, J.; Snyder, J. K., *Tetrahedron Lett.* **1987**, *28*, 3427.
27. Yang, B.; Liu, L.; Katz, T. J.; Liberko, C. A.; Miller, L. L., *J. Am. Chem. Soc.* **1991**, *113*, 8993.
28. Giorgi-Renault, S.; Renault, J.; Gebel-Servolles, P.; Baron, M.; Paoletti, C.; Cros, S.; Bissery, M.-C.; Lavelle, F.; Atassi, G., *J. Med. Chem.* **1991**, *34*, 38.
29. Castedo, L.; Puga, A.; Saa, J. M.; Suau, R., *Tetrahedron Lett.* **1981**, *22*, 2233.
30. Morey, J.; Dzielenziak, A.; Saa, J. M., *Chem. Lett.* **1985**, 263.
31. Garcia-Raso, A.; Deya, P. M.; Saa, J. M., *J. Org. Chem.* **1986**, *51*, 4285.

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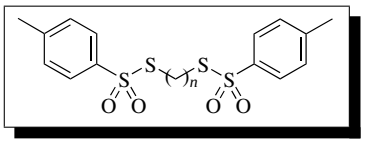
1,3-Propanedithiol Bis(*p*-toluenesulfonate)[1]



(*n* = 3)
[3866-79-3] $C_{17}H_{20}O_4S_4$ (MW 416.65)
InChI = 1/C17H20O4S4/c1-14-4-8-16(9-5-14)24(18,19)22-12-3-13-23-25(20,21)17-10-6-15(2)7-11-17/h4-11H,3,12-13H2,1-2H3
InChIKey = QOICHLMIPNOKLN-UHFFFAOYAN
(*n* = 2)
[2225-23-2] $C_{16}H_{18}O_4S_4$ (MW 402.62)
InChI = 1/C16H18O4S4/c1-13-3-7-15(8-4-13)23(17,18)21-11-12-22-24(19,20)16-9-5-14(2)6-10-16/h3-10H,11-12H2,1-2H3
InChIKey = DUFUGAKEFZRFEQ-UHFFFAOYAN

(dithianylation and dithiolanylation of methylene groups adjacent to carbonyl;[2] α,α-dithianyl cycloalkanones undergo oxidative ring scission;[3] oxidation of ketones to 1,2-diketones can be achieved by α,α-dithianylation or dithiolanation of ketones followed by hydrolysis[4])

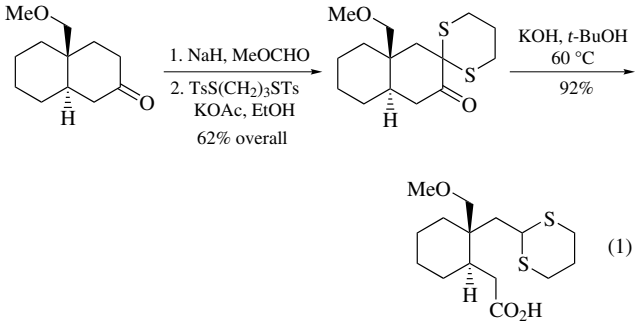
Physical Data: 1,3-propanedithiol bis(*p*-toluenesulfonate): mp 67 °C; 1,2-ethanedithiol bis(*p*-toluenesulfonate): mp 76 °C.

Preparative Methods: treatment of potassium thiotosylate, itself made by the reaction of *p*-toluenesulfonyl chloride with potassium hydrogen sulfide, with 1,3-dibromopropane or 1,2-dibromoethane in the presence of potassium iodide affords 1,3-propanedithiol bis(*p*-toluenesulfonate) and 1,2-ethanedithiol bis(*p*-toluenesulfonate), respectively.[5]

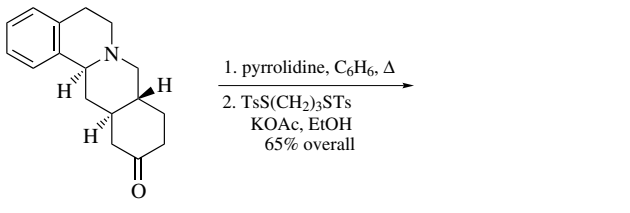
Oxidative Ring Cleavage of Cycloalkanones. Ketones can be α,α-dithianylated or α,α-dithiolanylated by treatment of their enamines or α-formyl derivatives with 1,3-propanedithiol or 1,2-ethanedithiol bis(*p*-toluenesulfonate), respectively.[1,2] Subjection of α,α-dithianyl ketones to potassium hydroxide in *t*-BuOH results in carbonyl carbon–dithiane carbon bond cleavage, affording ω-dithianyl acids (eq 1).[3] Presumably, a mechanism similar to the benzilic acid rearrangement is operative. Consistent with this assumption is the observation that easily enolizable and sterically hindered dithianyl ketones are inert to these conditions. The lack of examples of similar cleavage of α,α-dithiolanyl ketones may be related to the inability of dithiolanes to support anion formation.[6] Alternative methods for effecting this type of cleavage, such as ozonolysis of an enol derivative, frequently are poorly reproducible.

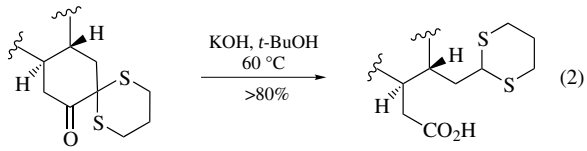
The exquisite regioselectivity possible in enamine formation or α-formylation of cycloalkanones, followed by α,α-dithianation and ring cleavage, has been exploited in several natural product syntheses (eqs 2–4).[7–10]

Addition of organometallics to the carbonyl carbon, followed by base cleavage of the resulting α,α-dithianyl carbinols, generates ω-dithianyl ketones (eq 5).[11]

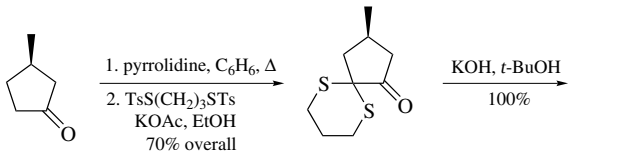


(1)

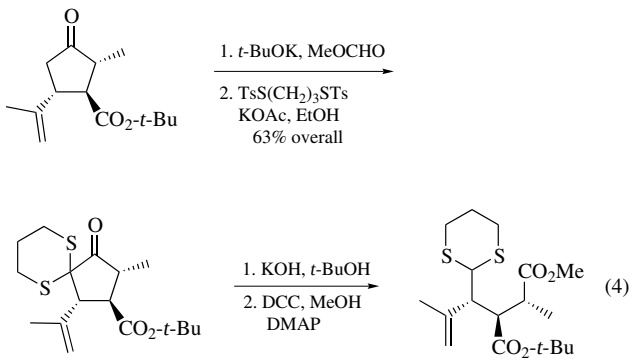




(2)

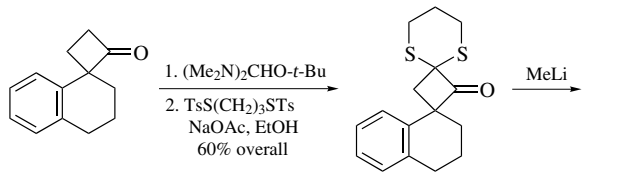


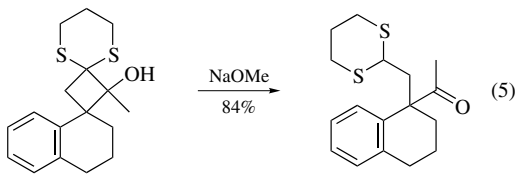
(3)



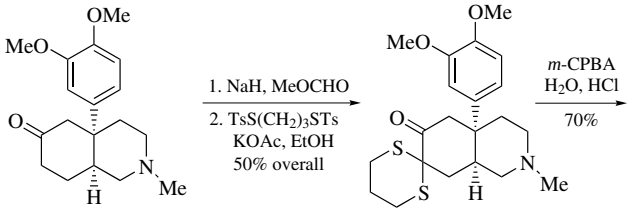
(4)

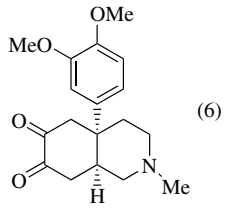
1,2-Carbonyl Transposition and Methylene Protection. Dithianes and dithiolanes can be removed under hydrolytic or reductive conditions. As α,α-dithianyl- and dithiolanylation of ketones effects oxidation of the α-carbon, hydrolytic removal of the protecting group affords 1,2-diketones (eq 6).[4,12] Chemical modification of the carbonyl carbon before hydrolytic removal of the dithiane or dithiolane effects 1,2-carbonyl transposition (eq 7).[13]



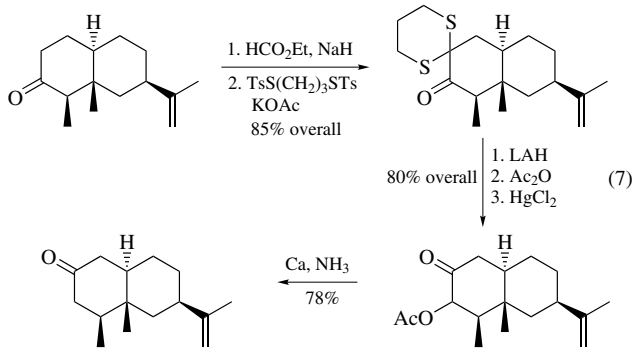


(5)



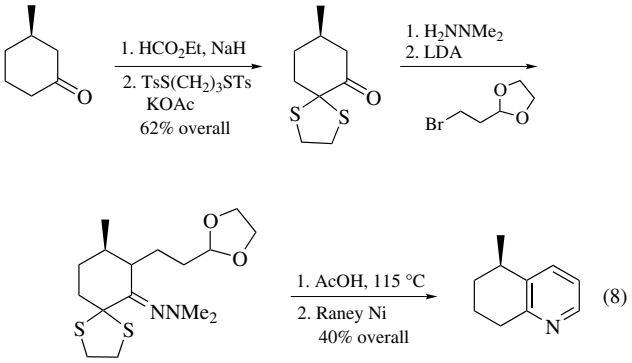


(6)



(7)

The ability to convert a dithianyl or dithiolanyl carbon to methylene by treatment with Raney nickel enables methylene protection α to a carbonyl. For example, the less enolizable α-methylene of a cycloalkanone can be alkylated by the sequence: (a) dithiolanylation of the more enolizable methylene; (b) enolization and alkylation at the remaining methylene; (c) reductive removal of the dithiolane group (eq 8).[14]



1. Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L., *J. Org. Chem.* **1971**, *36*, 1137.
2. (a) Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L., *Org. Synth.* **1974**, *54*, 39. (b) Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L., *Org. Synth.* **1974**, *54*, 37.
3. Marshall, J. A.; Seitz, D. E., *J. Org. Chem.* **1974**, *39*, 1814.
4. McMurry, J. E.; Farina, V., *Tetrahedron Lett.* **1983**, *24*, 4653.
5. Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L., *Org. Synth.* **1974**, *54*, 33.
6. Wilson, S. R.; Georgiadis, G. M.; Khatri, H. N.; Bartmess, J. E., *J. Am. Chem. Soc.* **1980**, *102*, 3577.
7. Takano, S.; Sasaki, M.; Kanno, H. Shishido, K.; Ogasawara, K., *J. Org. Chem.* **1978**, *43*, 4169.
8. Takano, S.; Masuda, K.; Ogasawara, K., *Heterocycles* **1981**, *16*, 1509.
9. Honda, T.; Ishizone, H.; Naito, K.; Wakako, M.; Suzuki, Y., *Chem. Pharm. Bull.* **1992**, *40*, 2031.
10. For other examples, see: (a) Marshall, J. A.; Seitz, D. E., *J. Org. Chem.* **1975**, *40*, 534. (b) Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K., *J. Am. Chem. Soc.* **1978**, *100*, 6218. (c) Trost, B. M.; Hiroi, K.; Jungheim, L. N., *J. Org. Chem.* **1980**, *45*, 1839.
11. Trost, B. M.; Preckel, M., *J. Am. Chem. Soc.* **1973**, *95*, 7862.
12. For other examples, see: (a) Bryant, R. J.; McDonald, E., *Tetrahedron Lett.* **1975**, *16*, 3841. (b) Dauben, W. G.; Walker, D. M., *J. Org. Chem.* **1981**, *46*, 1103.
13. Marshall, J. A.; Roebke, H., *J. Org. Chem.* **1969**, *34*, 4188.
14. Chelucci, G.; Cossu, S.; Scano, G.; Soccolini, F., *Heterocycles* **1990**, *31*, 1397.

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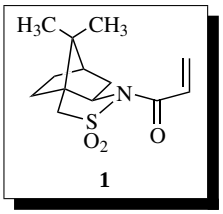
N-Propenoyl Camphor-10,2-sultam[1]



1

[94594-91-9] $C_{13}H_{19}NO_3S$ (MW 269.36)

InChI = 1/C13H19NO3S/c1-4-11(15)14-10-7-9-5-6-13(10,12(9,2)3)8-18(14,16)17/h4,9-10H,1,5-8H2,2-3H3/t9-,10?,13?/s2
InChIKey = QYWKUFBZHFLMBU-UWEUUAJCBU

(reagent used as a chiral acrylate derivative for various asymmetric organic reactions)

Physical Data: crystalline solid, mp 196–197 °C; $[\alpha]_D^{26}$ −100.9 (*c* 0.98, $CHCl_3$).

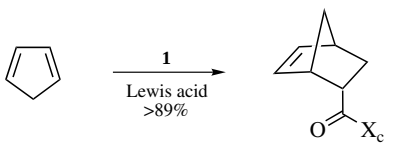
Solubility: soluble in most organic solvents.

Form Supplied in: available through synthesis.[2]

Handling, Storage, and Precaution: toxicity unknown; as with all organic chemicals, use of a well-ventilated fume hood is recommended.

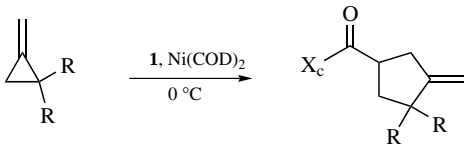
Introduction. Sultam derivative **1** ($X_cC(O)CH=CH_2$) has been exploited as a chiral auxiliary for a variety of reactions. Both antipodes are available in optically pure form from the chiral pool. Stereoselection of non-catalyzed reactions is usually consistent with the model advanced by Curran and co-workers[3] in which bond formation occurs at the *Re* face.

Cycloadditions. Oppolzer first used this chiral acrylate derivative as an auxiliary in the Diels–Alder reaction with cyclopentadiene. Promotion by Lewis acids such as $TiCl_4$ $SnCl_4$, and Et_2AlCl provides the adduct in greater than 90% de (eq 1).[2] Lithium perchlorate-promoted [4 + 2] reaction between **1** and 1-acetoxybutadiene was similarly effective.[4] More recently, an exo-selective Diels–Alder addition of **1** with 2-acylamino dienes provided a single diastereomer in 80% yield.[5] Cyclopentane formation is possible through exposure of **1** to methylenecyclopropane and Ni(0) (eq 2).[6] An example of a higher-order cycloaddition with **1** gave only low diastereoselection (78:22)[7] for the endo product.



(1)

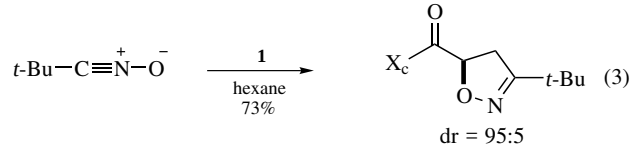
>90% de



(2)

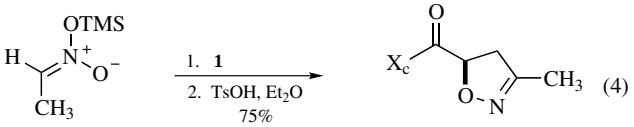
R = H — 86% de (76%)
R = CH_3 — 98% de (69%)

Both nitrile oxide (eq 3)[3] and silyl nitronate (eq 4)[8] cycloadditions are highly diastereoselective processes. The use of either approach enables access to Δ^2-isoxazolines in good yield. Unfortunately, the corresponding nitrone cycloadditions are only slightly selective (dr = 78:22)[9,10] The enantiomeric sultam was implemented effectively in azomethine ylide cycloadditions to gain access to bridged pyrrolidines with high levels of diastereoselection (eq 5).[11]



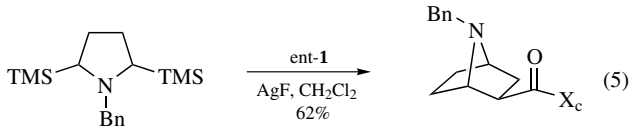
(3)

dr = 95:5



(4)

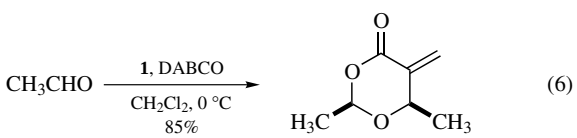
dr = 93:7



(5)

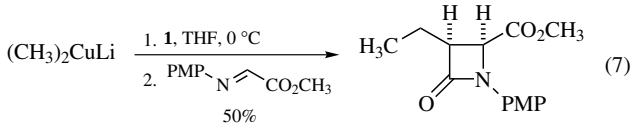
dr = 98:2

Carbon–Carbon Bond-forming Reactions. Several asymmetric ring-forming reactions using **1** have been developed to give products with high stereohomogeneity. In the Morita-Baylis-Hillman reaction of **1** with acetaldehyde, the auxiliary is cleaved in situ to give the hydroxy acid acetal in high ee (eq 6).[12] Michael addition to **1** followed by alkylation with an α-imino ester again results in cleavage of the auxiliary and formation of β-lactams stereoselectively (eq 7).[13,14] Cyclohexenes are conveniently accessed via palladium-mediated annulation (eq 8).[15]



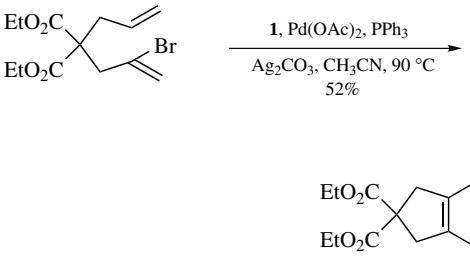
(6)

>99% ee



(7)

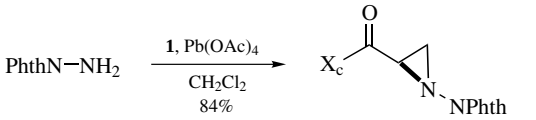
dr = 88:12
97% ee



(8)

>95% de

Oxidation. A single example involving aziridination of **1** has been reported, using *N*-aminophthalimide and Pb(IV) (eq 9). Good diastereoselection was observed (89:11) for production of the hydrazine derivative.[16]



(9)

1. (a) Oppolzer, W., *Pure Appl. Chem.* **1990**, *62*, 1241. (b) Kim, B. H.; Curran, D. P., *Tetrahedron* **1993**, *49*, 293.
2. Oppolzer, W.; Chapuis, C.; Bernardinelli, G., *Helv. Chim. Acta* **1984**, *67*, 1397.
3. Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A., *Tetrahedron Lett.* **1988**, *29*, 3555.
4. Mayer, S. C.; Pfizenmayer, A. J.; Cordova, R.; Li, W. R.; Joullie, M. M., *Tetrahedron: Asymmetry* **1994**, *5*, 519.
5. Ha, J. D.; Kang, C. H.; Belmore, K. A.; Cha, J. K., *J. Org. Chem.* **1998**, *63*, 3810.
6. Binger, P.; Schaefer, B., *Tetrahedron Lett.* **1988**, *29*, 529.
7. Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Henshilwood, J. A.; Short, K. M.; Sugathapala, P. M., *Tetrahedron* **1993**, *49*, 5495.
8. Kim, B. H.; Lee, J. Y., *Tetrahedron: Asymmetry* **1991**, *2*, 1359.
9. Tejero, T.; Dondoni, A.; Rojo, I.; Merchan, F. L.; Merino, P., *Tetrahedron* **1997**, *53*, 3301.
10. Merino, P.; Anoro, S.; Franco, S.; Merchan, F. L.; Tejero, T.; Tunon, V., *J. Org. Chem.* **2000**, *65*, 1590.
11. Pandey, G.; Laha, J. K.; Mohanakrishnan, A. K., *Tetrahedron Lett.* **1999**, *40*, 6065.
12. Brzezinski, L. J.; Rafel, S.; Leahy, J. W., *J. Am. Chem. Soc.* **1997**, *119*, 4317.
13. Palomo, C.; Aizpurua, J. M.; Gracenea, J. J.; Garcia-Granda, S.; Pertierra, P., *Eur. J. Org. Chem.* **1998**, 2201.
14. Palomo, C.; Aizpurua, J. M.; Gracenea, J. J., *J. Org. Chem.* **1999**, *64*, 1693.
15. (a) Ang, K. H.; Braese, S.; Steinig, A. G.; Meyer, F. E.; Llebaria, A.; Voigt, K.; de Meijere, A., *Tetrahedron* **1996**, *52*, 11503. (b) Voigt, K.; Lansky, A.; Noltemeyer, M.; de Meijere, A., *Liebigs Ann.* **1996**, 899.
16. Kapron, J. T.; Santarsiero, B. D.; Vederas, J. C., *J. Chem. Soc., Chem. Commun.* **1993**, 1074.

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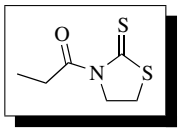
3-Propionylthiazolidine-2-thione[1]



[85260-51-1] $C_6H_9NOS_2$ (MW 175.30)

InChI = 1/C6H9NOS2/c1-2-5(8)7-3-4-10-6(7)9/h2-4H2,1H3

InChIKey = PFGBSLBKUIMZLZ-UHFFFAOYAF

(synthesis of β-hydroxy-α-methyl carboxylic esters, amides, and aldehydes,[2] propionate equivalent for the diastereo- and enantioselective aldol reactions[2,3])

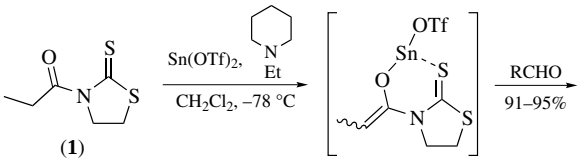
Physical Data: bp 151 °C/4 mmHg.

Form Supplied in: sticky, slightly yellow oil.

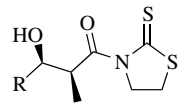
Preparative Methods: from propionyl chloride and 1,3-thiazolidine-2-thione in the presence of triethylamine, or from propionic acid and thiazolidine-2-thione in the presence of triethylamine and 2-chloro-1-methylpyridinium iodide.[4]

Handling, Storage, and Precautions: use in a fume hood.

Diastereoselective Aldol Reactions. The tin(II) enolate generated from 3-propionylthiazolidine-2-thione (**1**), tin(II) trifluoromethanesulfonate, and 1-ethylpiperidine reacts with aldehydes at −78 °C to afford the aldol adducts in high yields with high *syn* selectivities (eq 1).[2,3] 3-Acetylthiazolidine-2-thione (**2**) (bp 125–128 °C/2 mmHg)[2,3,5,8] and 3-(3-phenylpropanoyl)thiazolidine-2-thione (**3**) (mp 66.0–67.5 °C)[2–4] also work well under the same reaction conditions.[2,3]

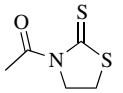


(**1**)

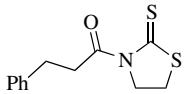


(1)

(**4**) *syn*:*anti* = >97:3

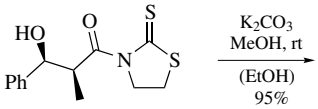


(**2**)

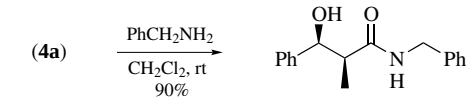


(**3**)

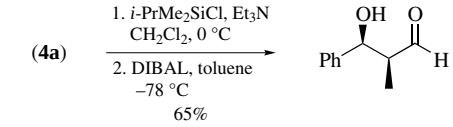
The aldol adducts (**4**) are easily converted to the corresponding β-hydroxy-α-methyl esters, amides, and aldehydes. Treatment of (**4**) (R = Ph) with methanol or ethanol in the presence of potassium carbonate at room temperature gives the methyl or ethyl ester in high yield (eq 2).[2] Similarly, the amide is spontaneously formed by mixing (**4**) with the amine in dichloromethane (eq 3).[2] The preparation of the aldehyde is carried out by using diisobutylaluminum hydride as a reductant after protection of the hydroxy function of (**4**) with the dimethylisopropylsilyl group (eq 4).[2,4] No isomerization occurs during these conversions.



(**4a**) (**4**; R = Ph) (2)



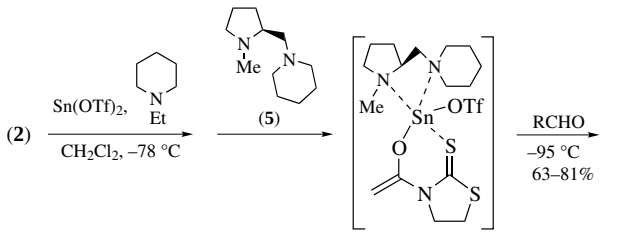
(**4a**) (3)



(**4a**) (4)

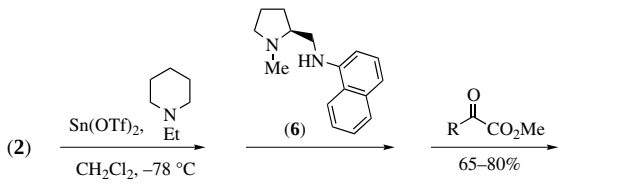
Enantioselective Aldol Reactions. A highly enantioselective aldol reaction of the tin(II) enolate derived from (**2**) with aldehydes is carried out in the presence of the chiral diamine (**5**) as a ligand (eq 5).[3,5,6] Aromatic and aliphatic ketones instead of (**2**) are good substrates in the present asymmetric aldol reaction,[3,7] and enantioselectivities are influenced strongly by the structure of the chiral diamines.

The tin(II) enolate of (**2**) reacts with α-keto esters in the presence of the chiral diamine (**6**) to give optically active 2-substituted malic acid ester derivatives in high yields with high ee (eq 6).[8]



(5)

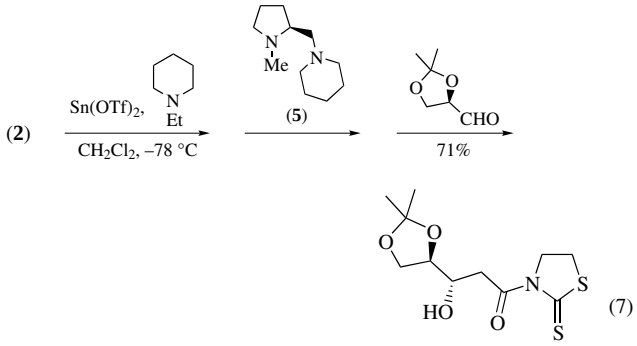
65–90% ee

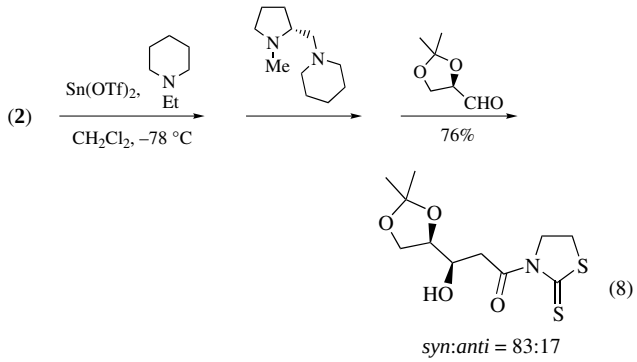


(6)

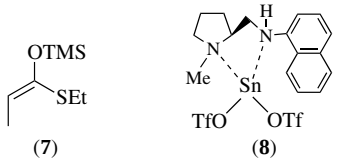
85–95% ee

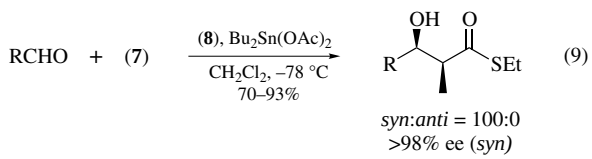
The tin(II) enolate of (**2**) also reacts with chiral aldehydes in the presence of (**5**). Diastereoselectivities can be controlled by the absolute configuration of the chiral diamines (eqs 7 and 8).[1f]



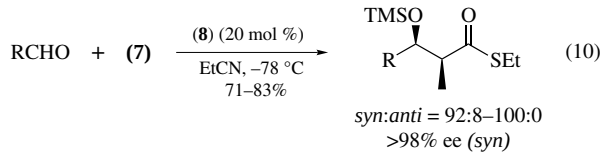


In the reaction of the tin(II) enolate derived from (**1**) with aldehydes, enantioselectivities are disappointingly low, while good diastereoselectivities are observed. Highly diastereo- and enantioselective aldol reactions of propionate derivatives with aldehydes have been achieved by using the ketene silyl thioacetal (**7**) instead of the tin(II) enolate. The complex (**8**) produced by mixing tin(II) triflate and the chiral diamine (**6**) works as an efficient chiral Lewis acid. The reaction of (**7**) with various aldehydes proceeds smoothly in the presence of (**8**) and dibutyltin diacetate in dichloromethane to afford the *syn* aldol adducts in high yields with almost perfect stereochemical control (eq 9).[9]





While stoichiometric amounts of tin(II) triflate, (**6**), and the tin(IV) compound are necessary in the reaction shown in eq 9, the truly catalytic asymmetric aldol reaction of (**7**) with aldehydes is realized by using (**8**) as a Lewis acid catalyst (eq 10).[10] The reaction is carried out in propionitrile by slow addition of the substrates to the catalyst.



Related Reagents. 3-(2-Benzyloxyacetyl)thiazolidine-2-thione; 2,6-Dimethylphenyl Propionate; 2-Methyl-2-(trimethylsilyloxy)-3-pentanone; 1,3-Thiazolidine-2-thione; Tin(II) Trifluoromethanesulfonate.

1. (a) Mukaiyama, T., *Pure Appl. Chem.* **1983**, *55*, 1749. (b) Mukaiyama, T., *Isr. J. Chem.* **1984**, *24*, 162. (c) Mukaiyama, T., *Chem. Scr.* **1985**, *25*, 13. (d) Mukaiyama, T.; Asami, M., *Top. Curr. Chem.* **1985**, *127*, 133. (e) Mukaiyama, T., *Pure Appl. Chem.* **1986**, *58*, 505. (f) Mukaiyama, T. *Challenges in Synthetic Organic Chemistry*; Oxford University Press: Oxford, 1990; p 191.
2. Mukaiyama, T.; Iwasawa, N., *Chem. Lett.* **1982**, 1903.
3. Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T., *Tetrahedron* **1984**, *40*, 1381.
4. (a) Izawa, T.; Mukaiyama, T., *Chem. Lett.* **1977**, 1443. (b) Izawa, T.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **1979**, *52*, 555.
5. Iwasawa, N.; Mukaiyama, T., *Chem. Lett.* **1983**, 297.
6. (a) Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869. (b) Mukaiyama, T., *Tetrahedron* **1981**, *37*, 4111.
7. Iwasawa, N.; Mukaiyama, T., *Chem. Lett.* **1982**, 1441.
8. Stevens, R. W.; Mukaiyama, T., *Chem. Lett.* **1983**, 1799.
9. (a) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T., *J. Am. Chem. Soc.* **1991**, *113*, 4247. (b) Mukaiyama, T.; Uchiro, H.; Kobayashi, S., *Chem. Lett.* **1989**, 1001. (c) Mukaiyama, T.; Uchiro, H.; Kobayashi, S., *Chem. Lett.* **1989**, 1757.
10. (a) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T., *Tetrahedron* **1993**, *49*, 1761. (b) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I., *Chem. Lett.* **1990**, 129. (c) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T., *Chem. Lett.* **1990**, 1455.

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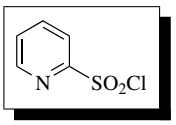
2-Pyridinesulfonyl Chloride



[66715-65-9] $C_5H_4ClNO_2S$ (MW 177.62)
InChI = 1/C5H4ClNO2S/c6-10(8,9)5-3-1-2-4-7-5/h1-4H
InChIKey = JQJOGAGLBDBMLU-UHFFFAOYAI

(heteroarylsulfonyl chloride for the formation of 2-pyridinesulfonate esters which are excellent metal-assisted leaving groups in S_N2 displacement reactions with magnesium halides,[2] as well as in elimination reactions;[2] alkyl 2-pyridinesulfonate esters are transformed into 2-alkylpyridines upon treatment with organometallic reagents[3])

Physical Data: colorless crystalline solid.

Solubility: sol chlorinated hydrocarbons and in dipolar aprotic solvents; insol cold water (gradual hydrolysis).

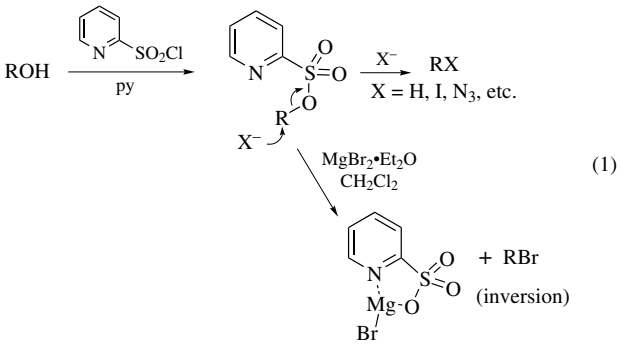
Preparative Method: prepared essentially according to the published procedure.[1] chlorine gas is bubbled into a solution of 2-pyridinethiol (4 g, 36 mmol) in concd. hydrochloric acid (32 mL) at 0 °C for 90 min. The solution is poured into ice–water (100 mL), and the precipitate is rapidly filtered and washed with ice-cold water (50 mL). The colorless crystalline product is dried at 0 °C (pump), then stored at 0 °C for use; yield 3.6 g (55%).

Handling, Storage, and Precautions: the crystalline reagent is stable when stored at 0 °C under argon for several months. Use in a fume hood.

Preparation of 2-Pyridinesulfonates.[2] The reagent (3.0 g, 3.5 mmol) is added in portions to a solution of the alcohol (3.00 mmol) in dry pyridine (5 mL) at 0 °C. After stirring for a few hours (cholestanol, 3 h; *t*-butylmethyl alcohol, 18 h), the solution is poured into ice–water and the 2-pyridinesulfonate is isolated by filtration in some cases. Otherwise, the aqueous solution is extracted with dichloromethane, which is then washed with dil. HCl and water and processed in the usual way. The 2-pyridinesulfonate is isolated by crystallization or by flash chromatography. For example, 2-pyridinesulfonates are prepared from cholestanol (quant.), mp 127–128 °C; 1,2:3,4-di-*O*-isopropylidene-D-galactose (97%), mp 89–90 °C; L-borneol (93%), mp 99–100 °C; *t*-butylmethanol (90%), mp 47 °C; 1-octanol (94%), 2-octanol (85%), and ethyl lactate (93%), isolated as oils.

Preparation of Alkyl Halides from 2-Pyridinesulfonates. The conceptual basis in designing novel nucleofugal esters such as 2-pyridinesulfonates was predicated upon the anticipation of an accelerated, metal-assisted S_N2 displacement reaction especially with divalent ions. Indeed, upon treatment of primary and secondary 2-pyridinesulfonates with magnesium bromide etherate (1.3 equiv) in dichloromethane at 0 °C, the corresponding bromides are obtained within seconds or minutes (eq 1).[2] With carbohydrate derivatives, the displacements are slower (several hours) presumably because of the presence of ether-type oxygen atoms which can also coordinate with the reagent. Comparisons of the reaction of various norbornyl sulfonates demonstrate the extremely efficient transformations using 2-pyridinesulfonates (1.3 equiv $MgBr_2$·Et_2O, 5 mL CH_2Cl_2): 8-quinolinesulfonate (120 min); tosylate (70 min); *p*-nitrobenzenesulfonate (40 min); 2-pyridinesulfonate (30 s, 70% of isolated bromide). Replacement of $MgBr_2$·Et_2O with other sources of bromide ion (lithium bromide, tetrabutylammonium bromide in DMF or CH_2Cl_2), requires heating and longer reaction times, while the addition of an external source of bromide does not accelerate the reaction.

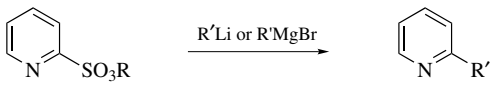
Typical products are 1-octyl bromide (0 °C, 5 min; 88%); 2-octyl bromide, $[\alpha]_D^{25}$ +33.4° (*c*, 4.23), (0 °C, 30 s, 74%); 2-benzyloxy-1-bromoethane (0 °C, 30 min, 94%); (*R*)-ethyl 2-bromopropionate, $[\alpha]_D^{25}$ +32.4° (*c*, 3.93), (0 °C, 10 min, 81%); *exo*-2-bromobicyclo[2,2,1] heptane, (0 °C, 30 s, 70%); and 3α-cholestanyl bromide, mp 102 °C, $[\alpha]_D^{25}$ +30° (*c*, 1.0), (0 °C, 5 min, 82%). Nucleophilic displacement reactions based on the remote activation of the nucleofugal component have also been demonstrated with alkyl imidazolylsulfonates,[4] and in the synthesis of *O*-, *C*-, and related glycosides.[5,6] Related heteroatom and metal-assisted S_N2 displacement reactions of tosylates have been recently reported.[7]



(1)

Miscellaneous Reactions of 2-Pyridinesulfonates. Other reactions well known for arenesulfonates are also possible with 2-pyridinesulfonates. For example, treatment of 3β-cholestanyl 2-pyridinesulfonate with sodium borohydride (DMF, 80 °C), lithium iodide (1,2-dichloroethane, 25 °C, 3 h), and LiN_3 (DMF, 80 °C, 4 h), gives cholestane (78%), 3α-iodocholestane (76%), and 3α-azidocholestane (63%), respectively.[8] Treatment of 3β-cholestanyl 2-pyridinesulfonate with palladium(II) chloride (2 equiv) in DMF (80 °C, 30 min), gives 2-cholestene (80%).[9]

2-Substituted Pyridines. Although there are examples of the synthesis of 2-alkylpyridines[10] by direct and indirect methods, the yields in some cases are low and the conditions harsh. Treatment of alkyl 2-pyridinesulfonates (methyl, propyl, *t*-butylmethyl) with butyllithium, *n*-butylmagnesium bromide, allylmagnesium bromide, and phenyllithium at −78 °C (lithium reagents) or at 0 °C (Grignard reagents), gives the corresponding 2-substituted pyridines in 68–80% yields (eq 2). In principle, any alkyl 2-pyridinesulfonate can be used. However, for convenience of handling, the crystalline *t*-butylmethyl 2-pyridinesulfonate can be used.



(2)

Related Reagents. Benzenesulfonyl Chloride; 4-Bromobenzenesulfonyl Chloride; Mesitylenesulfonyl Chloride; *p*-Toluenesulfonyl Chloride.

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1. Falik, Z.; Plazek, E., *Acta Pol. Pharm.* **1955**, *12*, 5 (*Chem. Abstr.* **1957**, *51*, 17 911c); see also Caldwell, W. T.; Kornfeld, E. C., *J. Am. Chem. Soc.* **1942**, *64*, 1695 for the preparation of 5-acetamido-2-pyridinesulfonyl chloride.
2. Hanessian, S.; Kagotani, M.; Komaglo, K., *Heterocycles* **1989**, *28*, 1115.
3. Hanessian, S.; Kagotani, M., *Synthesis* **1987**, 409.
4. Hanessian, S.; Vatèle, J.-M.; *Tetrahedron* **1981**, *22*, 3579.
5. Hanessian, S.; Bacquet, C.; LeHong, P., *Carbohydr. Res.* **1980**, *80*, C17.
6. Stewart, A. O.; Williams, R. M., *J. Am. Chem. Soc.* **1985**, *107*, 4289.
7. Hanessian, S.; Thavonekham, B.; Dehoff, B., *J. Org. Chem.* **1989**, *54*, 5831.

8. For a discussion of reactions occurring via prior coordination, see, Beak, P.; Meyers, A. I., *Acc. Chem. Res.* **1986**, *19*, 356.
9. Place, P.; Roumestant, M.-L.; Goré, J.; *Bull. Soc. Chem. Fr. Part 2* **1975**, 169.
10. Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 2, p 262.

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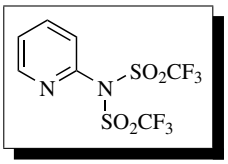
N-(2-Pyridyl)bis(trifluoromethanesulfonimide)



[145100-50-1] $C_7H_4F_6N_2O_4S_2$ (MW 358.24)
InChI = 1/C7H4F6N2O4S2/c8-6(9,10)20(16,17)15(5-3-1-2-4-14-5)21(18,19)7(11,12)13/h1-4H
InChIKey = DXLQEJHUQKKSRB-UHFFFAOYAU

(triflating agent, vinyl triflate formation from thermodynamic and kinetic enolates generated by deprotonation, formation of aryl triflates)

Alternate Names: 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-pyridine; *N*,*N*-bis(trifluoromethylsulfonyl)-2-pyridylamine; *N*-(2-pyridyl)triflimide.

Physical Data: mp 40–42 °C; bp 80–90 °C/0.25 mmHg; fp 230 °F (110 °C).

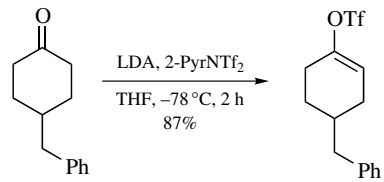
Form Supplied in: pale yellow solid (crystals).

Preparative Methods: *N*-(2-pyridyl)bis(trifluoromethanesulfonimide) [2-PyrNTf$_2$] is prepared from 2-aminopyridine and triflic anhydride.[1] To a solution of 2-aminopyridine (19.8 g, 0.210 mol, 1.0 equiv) and pyridine (35.0 g, 0.443 mol, 2.1 equiv) in CH_2Cl_2 (800 mL) at −78 °C is added triflic anhydride (125.0 g, 74.5 mL, 0.443 mol, 2.1 equiv) in CH_2Cl_2 (150 mL). After 2 h at −78 °C, the cooling bath is removed and the stirring is continued at rt for 19 h. The reaction mixture is quenched with water (50 mL) and the aqueous layer is extracted with CH_2Cl_2 (4 × 50 mL). The organic extracts are washed with sodium hydroxide (150 mL), cold water (100 mL), brine (100 mL), and dried over $MgSO_4$. After filtration, the solvent is removed under vacuum to give 69.0 g of the crude product. Distillation gives pure 2-PyrNTf$_2$ in 80% yield.

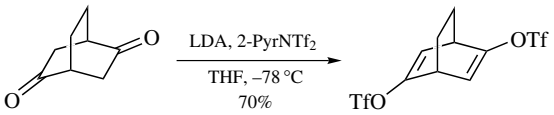
Purification: distillation.

Handling, Storage, and Precautions: stable; should be handled with care; irritant for eyes, skin, and respiratory system.

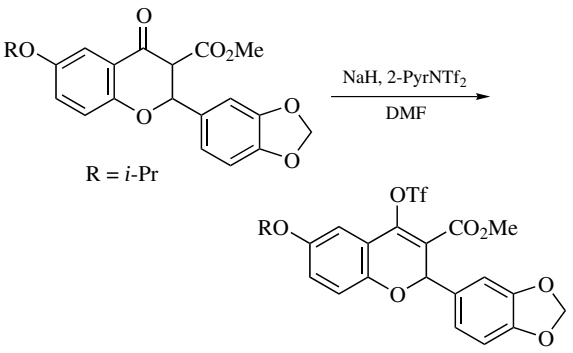
Formation of Enol Trifluoromethanesulfonates (Enol Triflates). *N*-(2-Pyridyl)bis(trifluoromethanesulfonimide) is highly reactive but easy to handle for the production of vinyl triflates. In most cases 2-PyrNTf$_2$ proved to be substantially more reactive than *N*-phenyltriflimide allowing the majority of vinyl triflates to be prepared at −78 °C in only 2–4 h.[1] The enolates are produced by treatment of ketones with various bases such as NaH or KH, LDA, NaHMDS, LiHMDS, or KHMDS in THF, DMF, or DME, followed by the addition of 2-PyrNTf$_2$ to afford the vinyl triflates in good to excellent yield[2–8] (eqs 1–3).



(1)

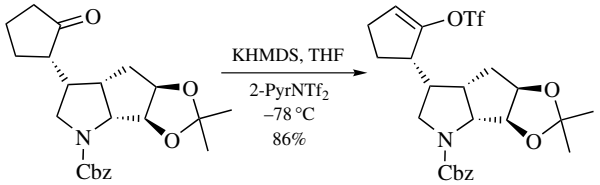


(2)

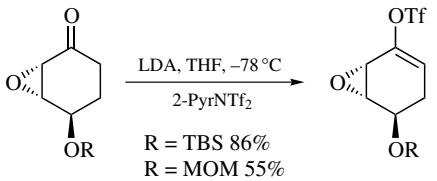


(3)

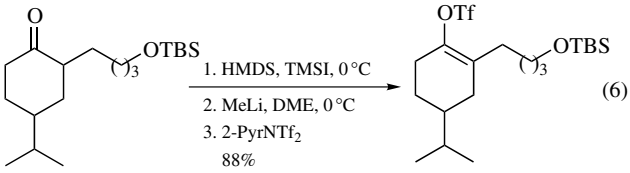
Regiospecific Generation of Enol Triflates. Kinetic and thermodynamic enolates, generated directly by treatment of ketones with a base (eqs 4 and 5) or from regio-defined silyl enol ethers by treatment with MeLi (eq 6), react with 2-PyrNTf$_2$ to give the corresponding vinyl triflates. 2-PyrNTf$_2$ has been used in the total synthesis of magellamine[9] and (±)-saudin,[10] nupharamine,[11] and in an approach to acromelic acids,[12] (±)-mesembranol,[13] (±)-erythrodiene,[14] (±)-spirojatamol,[14] and the C12–C19 fragment of amphidinol E.[15]



(4)

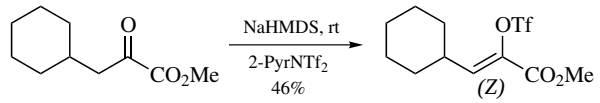


(5)

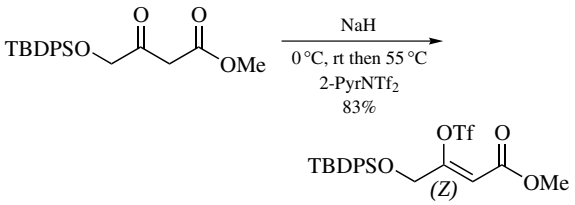


(6)

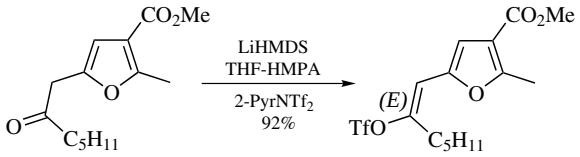
Acyclic ketones can be stereoselectively transformed to enol triflates under kinetic or thermodynamic conditions (eqs 7–9).[2,16–18]



(7)



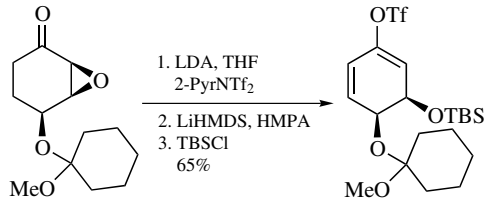
(8)



(9)

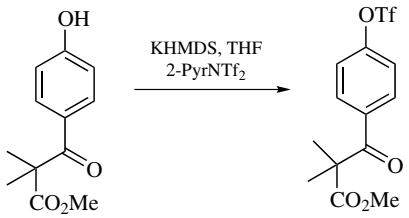
The A-ring of 1α,25-dihydroxy-22-oxavitamin D3[17] and all-*trans*-geranylgeraniol[16] have been prepared from stereo-defined enol triflates synthesized from ketones by using 2-PyrNTf$_2$.

Dienic Enol Triflates. Enone enolates generated from epoxyketones are also reactive with 2-PyrNTf$_2$ to provide dienic enol triflates in good yield[19] (eq 10).



(10)

Aryl Triflates. 2-PyrNTf$_2$ has been used to transform phenols to aryl triflates[20] (eq 11).



(11)

Utility of Enol and Aryl Triflates. Enol triflates have been utilized to generate vinyl cations, carbenes,[21,22] and 1,2,3-cyclohexatriene.[23] Enol triflates undergo coupling with diorganocuprates.[24] Palladium-catalyzed coupling with organometallics, alkynes, and alkenes, as well as carbonylation, can be achieved with enol and aryl triflates.[25,26] Palladium-catalyzed transformation of enol triflate to olefins[2,16] and aryl triflates to aniline[20] have also been realized.

Related Reagents. *N*,*N*-Phenyltrifluoromethanesulfonimide; 2-[*N*, *N*-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' Reagent).

1. Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P., *Org. Synth.* **1997**, *74*, 77.
2. Gebauer, O.; Bruckner, R., *Synthesis* **2000**, *4*, 588.
3. Comins, D. L.; Dehghani, A., *Tetrahedron Lett.* **1992**, *33*, 6299.
4. Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T., *J. Am. Chem. Soc.* **2004**, *126*, 13584.
5. Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K., *J. Am. Chem. Soc.* **2003**, *125*, 11508.
6. Campbell, J. A.; Lee, W. K.; Rapoport, H., *J. Org. Chem.* **1995**, *60*, 4602.
7. Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T., *J. Org. Chem.* **2005**, *70*, 2503.
8. Ishizuka, N.; Matsumura, K.; Sakai, K.; Fujimoto, M.; Mihara, S.; Yamamori, T., *J. Med. Chem.* **2002**, *45*, 2041.
9. Yen, C.-F.; Liao, C.-C., *Angew. Chem., Int. Ed.* **2002**, *41*, 4090.
10. Winkler, J. D.; Doherty, E. M., *J. Am. Chem. Soc.* **1999**, *121*, 7425.
11. Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C., *J. Org. Chem.* **1999**, *64*, 3736.
12. Nakagawa, H.; Sugahara, T.; Ogasawara, K., *Tetrahedron Lett.* **2001**, *42*, 4523.
13. Evarts, J. B.; Fuchs, P. L., *Tetrahedron Lett.* **2001**, *42*, 3673.
14. Tokunaga, Y.; Yagihashi, M.; Ihara, M.; Fukumoto, K., *J. Chem. Soc., Chem. Commun.* **1995**, *9*, 955.
15. Gurjar, M. K.; Mohapatra, S.; Phalgune, U. D.; Puranik, V. G.; Mohapatra, D. K., *Tetrahedron Lett.* **2004**, *45*, 7899.
16. Mu, Y.; Gibbs, R. A., *Tetrahedron Lett.* **1995**, *36*, 5669.
17. Hatakeyama, S.; Okano, T.; Maeyama, J.; Esumi, T.; Hiyamizu, H.; Iwabuchi, Y.; Nakagawa, K.; Ozono, K.; Kawase, A.; Kubodera, N., *Bioorg. Med. Chem.* **2001**, *9*, 403.
18. Marshall, J. A.; Zou, D., *Tetrahedron Lett.* **2000**, *41*, 1347.
19. Evarts, J. B.; Fuchs, P. L., *Tetrahedron Lett.* **1999**, *40*, 2703.
20. Edmondson, S. D.; Mastracchio, A.; He, J.; Chung, C. C.; Forrest, M. J.; Hofsees, S.; MacIntyre, E.; Metzger, J.; O'Connor, N.; Patel, K.; Tong, X.; Tota, M. R.; Van der Ploeg, L. H. T.; Varnerin, J. P.; Fisher, M. H.; Wyvratt, M. J.; Weber, A. E.; Parmee, E. R., *Bioorg. Med. Chem.* **2003**, *13*, 3983.
21. Stang, P. J., *Acc. Chem. Res.* **1978**, *11*, 107.
22. Stang, P. J.; Hanack, M.; Subramanian, L. R., *Science* **1982**, 85.
23. Shakespeare, W. C.; Johnson, R. P., *J. Am. Chem. Soc.* **1990**, *112*, 8578.
24. Castelani, P.; Comasseto, J. V., *Organometallics* **2003**, *22*, 2108.
25. Ceccarelli, S.; Piarulli, U.; Gennari, C., *J. Org. Chem.* **2000**, *65*, 6254.
26. Okauchi, T.; Yano, T.; Fukamachi, T.; Ichiwaka, J.; Minami, T., *Tetrahedron Lett.* **1999**, *40*, 5337.

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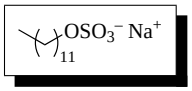
S

Sodium Dodecyl Sulfate



[151-21-3] $C_{12}H_{25}NaO_4S$ (MW 288.38)

InChI = 1/C12H26O4S.Na/c1-2-3-4-5-6-7-8-9-10-11-12-16-17(13,14)15);/h2-12H2,1H3,(H,13,14,15);/q;+1/p-1//fC12H25O4S.Na/q-1;m

InChIKey = DBMJMQXJHONAFJ-AITAGSLOCU

(used in surfactant-based reaction media)

Alternate Names: SDS; sodium lauryl sulfate; SLS.

Physical Data: mp 204–207 °C.

Solubility: sol H_2O; insol Et_2O; critical micelle concentration (CMC) in H_2O (25 °C) = 8.1 mM.[1]

Form Supplied in: colorless or white solid.

Analysis of Reagent Purity: commercially available sodium dodecyl sulfate generally contains 1-dodecanol,[2] which yields a minimum at the CMC in plots of surface tension vs. concentration. The presence of 1-dodecanol can be detected by an HPLC method.[3] Impurities can also include surfactant homologs and electrolytes,[2] which yield low surface tension values above the CMC.

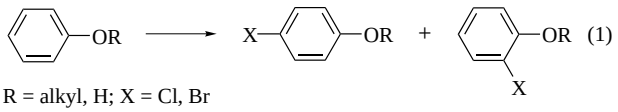
Preparative Methods: by sulfation of 1-dodecanol with sulfur trioxide, followed by neutralization of the resultant dodecylsulfuric acid with sodium hydroxide.[4]

Purification: recrystallization from H_2O and EtOH.[5]

Handling, Storage, and Precautions: harmful if inhaled or swallowed and is irritating to the eyes and skin; should be stored under nitrogen.[2b]

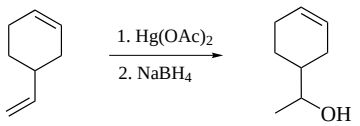
General Considerations. In H_2O, SDS forms micelles above its CMC. Aqueous micellar solutions solubilize neutral organic compounds that would otherwise be insoluble in H_2O alone. Synthetic applications of micellar SDS have generally involved its ability to solubilize simultaneously both H_2O-insoluble organic substrates and H_2O-soluble (inorganic) reagents, and thus to facilitate their reactions under homogeneous conditions. An organic compound with even modest polarity is normally solubilized within a micelle in a preferred time-averaged orientation with the polar portion near or at the micelle–H_2O interface and the nonpolar portion directed into the micelle's hydrocarbon interior. In several of the examples given below, regioselectivity has resulted from these orientational effects. The features and principles of micellar catalysis have been reviewed,[6] including coulombic attraction and repulsion of ionic reagents from charged micelle–H_2O interfaces. SDS can also be used to form microemulsions, which are isotropic, optically transparent dispersions of oil (hydrocarbon) in water or water in oil. Microemulsions are formed from specific proportions of a surfactant, a cosurfactant (usually a low molecular weight alcohol), H_2O, and a hydrocarbon. Compared to aqueous micellar solutions, microemulsions can solubilize greater amounts of H_2O-insoluble organic compounds and thus offer greater reaction capacity.

Electrophilic Aromatic Substitution. Micellar SDS has been used as a reaction medium for the chlorination and bromination of alkyl phenyl ethers[4,5a,7] and phenol[7b,8] by several halogenating agents (eq 1). Compared to reactions in H_2O alone, the *para*:*ortho* product ratio increased for pentyl, nonyl, and dodecyl phenyl ether, and decreased for anisole. Enhanced *ortho* relative to *para* substitution was obtained with phenol. In each case the observed regioselectivity derived at least in part from alignment of the substrate at the micelle–H_2O interface and resultant differential steric shielding of the *para* and *ortho* positions by the micelle superstructure.



R = alkyl, H; X = Cl, Br (1)

Electrophilic Addition to Alkenes. Hydroxy- and alkoxymercurations of alkenes have been performed in micellar SDS.[9] Hydroxymercuration of (**1**) with mercury(II) acetate, followed by reduction with sodium borohydride, gave a greatly enhanced yield of (**2**) in micellar SDS (90%) relative to that obtained in THF–H_2O (20–25%) (eq 2).[9a] Also, the reactions of (**1**) and the related limonene[9a] gave greater cyclic ether:diol product ratios in the SDS environment than in aq THF. Both the enhanced yields and ratios were attributed to anisotropic solubilization of the alkylmercurial intermediate in a relatively H_2O-poor micellar microenvironment. The hydroxymercuration of an aromatic diene, *p*-diallylbenzene, did not display enhanced chemoselectivity (mono vs. diol formation) in micellar SDS relative to that obtained in THF–H_2O.[9b] This result suggests that the micellar solubilization sites of aromatic substrates and reaction intermediates are more H_2O-rich than those of aliphatic systems.



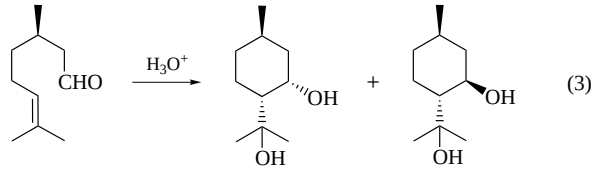
(**1**) (**2**) (2)

Alkoxymercuration of 1-octene in micellar SDS by added primary alcohols gave 2-octyl alkyl ethers.[9b] Thus when a given alcohol cannot be employed as both the reactant and solvent in the alkoxymercuration of an alkene, the use of micellar SDS–alcohol could be an attractive option.

Oxidation and Reduction. Hypochlorite oxidations of alcohols to aldehydes and acids and of primary amines to nitriles have been performed in micellar SDS.[10,11] A microemulsion composed of SDS, 1-butanol, H_2O, and cyclohexane has been used for the very rapid oxidation of ethyl 2-chloroethyl sulfide to the corresponding sulfone by hypochlorite.[12] SDS has been used as a catalyst in the oxidations of 3,6-dimethoxydurene and xylenes by

cerium(IV) ammonium nitrate under two-phase conditions.[13] Selective reductions of α,β-unsaturated aldehydes and ketones have been performed with $NaBH_4$ in micellar SDS.[14] Compared to reactions in EtOH and H_2O, greater fractions of unsaturated alcohols were obtained, relative to saturated alcohols.

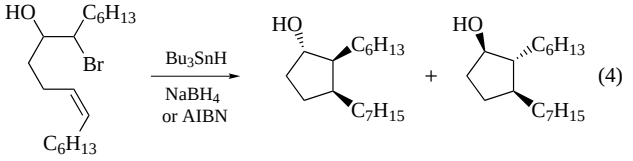
Cyclization. The acid-catalyzed cyclization of (+)-citronellal (**3**) in H_2O gives diols (**4**) and (**5**) (2:1 ratio) as the major products (eq 3).[15a] In micellar SDS, the product ratio increases to 5:1 and the rate of cyclization also increases.[15a] The product and rate effects in micellar SDS are consistent with orientational effects for reactive conformations of (**3**) at the micelle–H_2O interface. Furthermore, the cyclization can be performed in micellar SDS with concentrations of (**3**) far above its solubility in H_2O alone. Micellar SDS significantly altered the ratio of acyclic to cyclic alcohol products in the acid-catalyzed solvolysis of linalyl acetate.[15b]



(3)

(**3**) (**4**) (**5**)

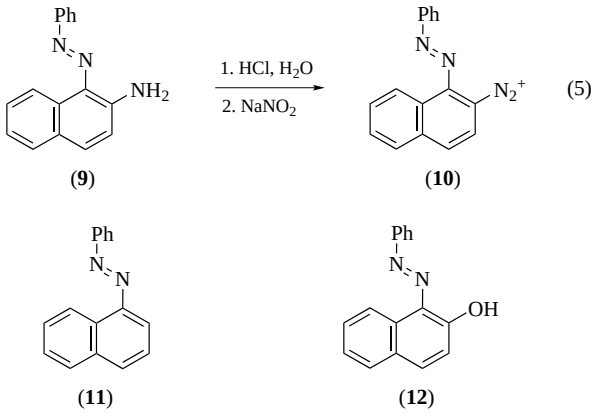
In micellar SDS and vesicular dipalmitoylphosphatidylcholine (DPPC), the aggregate–H_2O interfaces induce stereoselectivity in the radical cyclization of bromohydrin (**6**) (eq 4).[16] In C_6H_6 and pH 10 buffer the (**7**):(**8**) ratios are 0.77 and 1.03, respectively, whereas in the pH 10 buffer with SDS and DPPC the (**7**): (**8**) ratios are 2.29 and 2.39, respectively. These results are consistent with differential stabilization at the aggregate–H_2O interfaces of the diastereomeric transition states leading to (**7**) and (**8**).



(4)

(**6**) (**7**) (**8**)

Miscellaneous. Diazonium ion (**10**), formed from amine (**9**) (eq 5), in the presence of H_3PO_2 gives (**11**) with, and (**12**) without, micellar SDS.[17]

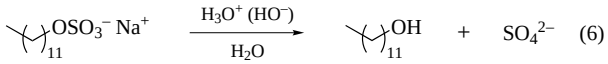


(5)

(**9**) (**10**)

(**11**) (**12**)

There have been many other reports of reactions of organic substrates performed in micellar SDS under conditions that would not be synthetically useful.[6] Generally, the focus of these studies has been kinetics and/or regio- and stereoselectivity. However, the clear potential exists for the application of their results to organic synthesis. The conditions under which SDS undergoes acid- and base-catalyzed hydrolyses (eq 6) are generally more severe than those used in reactions performed in micellar SDS;[18] thus the hydrolysis of SDS can usually be neglected.



(6)

Synthetic Application of Other Surfactants. In most cases, other anionic surfactants would be expected to offer results comparable to those obtained above with SDS. Cationic surfactants such as hexadecyltrimethylammonium bromide catalyze reactions involving anionic reagents.[6] In general, the isolation of organic products from surfactant-based reaction media can be facilitated by the use of cleavable surfactants.[19] A cleavable surfactant can be converted into nonsurfactant products after its use in a surfactant-based reaction solvent, thereby eliminating problems resulting from the presence of a surfactant during workup, such as the formation of persistent emulsions.

1. Mukerjee, P.; Mysels, K. J., *Nat. Stand. Ref. Data Ser.* **1971**, *NSRDS-NBS 36*, 66.
2. (a) Vijayendran, B. R., *J. Colloid Interface Sci.* **1977**, *60*, 418. (b) Smith, A., *J. Colloid Interface Sci.* **1978**, *66*, 575.
3. Czichocki, G.; Vollhardt, D.; Much, H., *J. Colloid Interface Sci.* **1983**, *95*, 275.
4. Jaeger, D. A.; Robertson, R. E., *J. Org. Chem.* **1977**, *42*, 3298.
5. (a) Jaeger, D. A.; Wyatt, J. R.; Robertson, R. E., *J. Org. Chem.* **1985**, *50*, 1467. (b) Mukerjee, P.; Cardinal, J. R., *J. Phys. Chem.* **1978**, *82*, 1620.
6. (a) Fendler, J. H.; Fendler, E. J. *Catalysis in Micellar and Macromolecular Systems*; Academic: New York, 1975. (b) Fendler, J. H. *Membrane Mimetic Chemistry*; Wiley: New York, 1982.
7. (a) Jaeger, D. A.; Clennan, M. W.; Jamrozik, J., *J. Am. Chem. Soc.* **1990**, *112*, 1171. (b) Onyiriuka, S. O.; Suckling, C. J., *J. Org. Chem.* **1986**, *51*, 1900.
8. (a) Onyiriuka, S. O.; Suckling, C. J.; Wilson, A. A., *J. Chem. Soc., Perkin Trans. 2* **1983**, 1103. (b) Onyiriuka, S. O.; Suckling, C. J., *J. Chem. Soc., Chem. Commun.* **1982**, 833. (c) Onyiriuka, S. O., *Bioorg. Chem.* **1986**, *14*, 97.
9. (a) Link, C. M.; Jansen, D. K.; Sukenik, C. N., *J. Am. Chem. Soc.* **1980**, *102*, 7798. (b) Sutter, J. K.; Sukenik, C. N., *J. Org. Chem.* **1982**, *47*, 4174. (c) Sutter, J. K.; Sukenik, C. N., *J. Org. Chem.* **1984**, *49*, 1295. (d) Livneh, M.; Sutter, J. K.; Sukenik, C. N., *J. Org. Chem.* **1987**, *52*, 5039.
10. Jursic, B., *Synthesis* **1988**, 868.
11. Jursic, B., *J. Chem. Res. (S)* **1988**, 168.
12. Menger, F. M.; Elrington, A. R., *J. Am. Chem. Soc.* **1990**, *112*, 8201.
13. Skrzewski, J.; Cichacz, E., *Bull. Chem. Soc. Jpn.* **1984**, *57*, 271.
14. Jursic, B.; Sunko, D. E., *J. Chem. Res. (S)* **1988**, 202.
15. (a) Clark, B. C. Jr., Chamblee, T. S.; Iacobucci, G. A., *J. Org. Chem.* **1984**, *49*, 4557. (b) Clark, B. C., jr.; Chamblee, T. S.; Iacobucci, G. A., *J. Org. Chem.* **1989**, *54*, 1032.
16. Wujek, D. G.; Porter, N. A., *Tetrahedron* **1985**, *41*, 3973.
17. Abe, M.; Suzuki, N.; Ogino, K., *J. Colloid Interface Sci.* **1983**, *93*, 285.

18. (a) Kurz, J. L., *J. Phys. Chem.* **1962**, *66*, 2239. (b) Garnett, C. J.; Lambie, A. J.; Beck, W. H.; Liler, M., *J. Chem. Soc., Faraday Trans. 1* **1983**, *79*, 953.
19. Jaeger, D. A.; Jamrozik, J.; Golich, T. G.; Clennan, M. W.; Mohebalian, J., *J. Am. Chem. Soc.* **1989**, *111*, 3001, and references therein.

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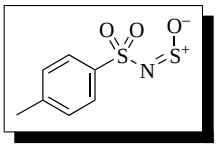
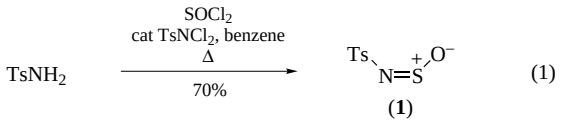
N-Sulfinyl-*p*-toluenesulfonamide[1]



[4104-47-6] $C_7H_7NO_3S_2$ (MW 217.29)
InChI = 1/C7H7NO3S2/c1-6-2-4-7(5-3-6)13(10,11)8-12-9/h2-5H,1H3
InChIKey = VKTSIMMJOIPMGE-UHFFFAOYAX

(used to generate electrophilic *N*-tosyl aldimines;[4–7] can act as an enophile in ene reactions[2,8] and as a dienophile in Diels–Alder reactions;[10,11] participates in Wittig-type reactions[17])

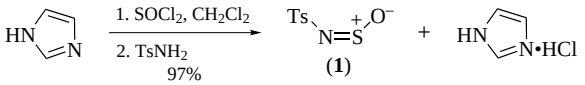
Alternate Name: 4-methyl-*N*-sulfinylbenzenesulfonamide.
Physical Data: mp 53 °C; bp 130–140 °C/0.06 mmHg.
Solubility: sol benzene, toluene, halogenated solvents.
Form Supplied in: bright yellow solid; commercially available.
Preparative Methods: the most common method of preparing *N*-sulfinyl-*p*-toluenesulfonamide (TsNSO) (**1**) is by heating *p*-toluenesulfonamide with excess thionyl chloride in benzene (eq 1).[2]



(1)

(**1**)

An alternative procedure is the treatment of *p*-toluenesulfonamide with *N*-chlorosulfinylimidazole, which is derived from thionyl chloride and imidazole (eq 2).[3] The latter method benefits from shorter reaction times and better yields.

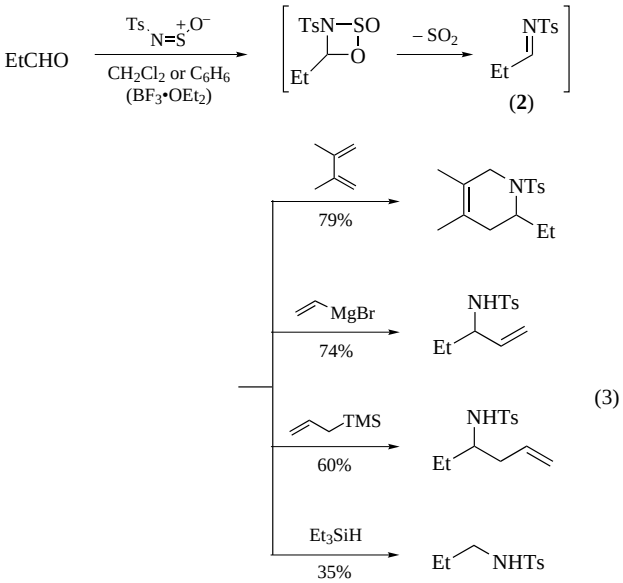


(2)

(**1**)

Handling, Storage, and Precautions: should be weighed out in a glove bag or dry box, since it readily hydrolyzes to *p*-toluenesulfonamide. Can be prepared just prior to use and used in situ or stored for extended periods of time in an inert environment.

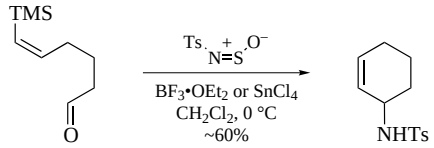
Formation of *N*-Tosyl Aldimines. A number of years ago it was reported by Kresze that nonenolizable aldehydes could be converted to the corresponding *N*-tosylimine using the title reagent (**1**) in the presence of a Lewis acid.[4] Recently, it has been shown that this transformation can also be effected with enolizable aldehydes both under Lewis acid catalysis at low temperature and thermally.[5] Thus treatment of propionaldehyde with (**1**) leads to the *N*-tosyl aldimine (**2**) or its Lewis acid complex (eq 3).



(3)

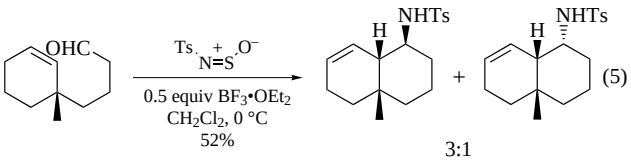
(**2**)

The imines (**2**) can be trapped in situ with 1,3 dienes,[5a] organometallic reagents,[5b] allyl silanes,[5c] or reduced with triethylsilane (eq 3).[5d] Vinyl silanes also add intramolecularly to *N*-tosylimines in the presence of boron trifluoride etherate or tin(IV) chloride to give cyclohexenylsulfonamides (eq 4).[6]



(4)

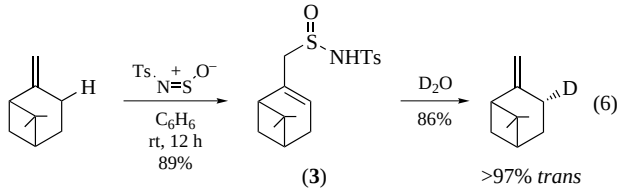
Intramolecular 'ene-like' reactions of Lewis acid complexed *N*-tosyliminium intermediates can be effected to afford cyclization products, presumably via a cationic, stepwise pathway (eq 5).[7]



(5)

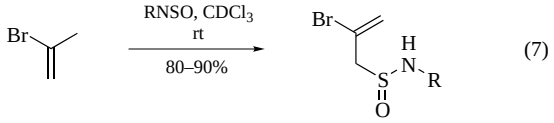
3:1

Ene Reaction. The ene reaction of (**1**) and β-pinene in benzene at rt to give the *N*-tosylsulfinamide (**3**) (eq 6)[2a] is reversible under these conditions and has been exploited specifically to introduce deuterium into the allylic position of an alkene.



(6)

A more reactive *N*-sulfinyl compound, *N*-sulfinylnonafluorobutanesulfonamide, undergoes intermolecular ene reactions with alkenes over 10^3 times faster than the corresponding tosyl derivative (eq 7).[8]

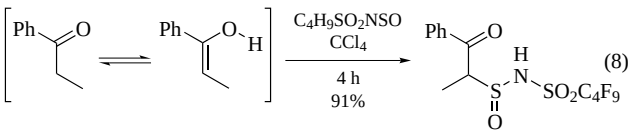


(7)

R = Ts, $\tau_{1/2}$ = 12000 min

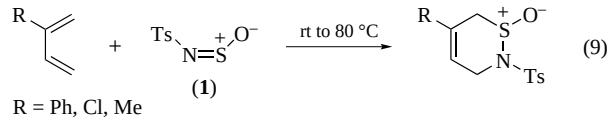
R = $C_4F_9SO_2$, $\tau_{1/2}$ = 5 min

In addition, this perfluoro-*N*-sulfinyl compound undergoes thermal, intermolecular ene reactions with 1-aryl-2-alkanones under neutral conditions to give *N*-sulfinyl-2-oxoalkanesulfonamides in high yields (eq 8).[8a,9]

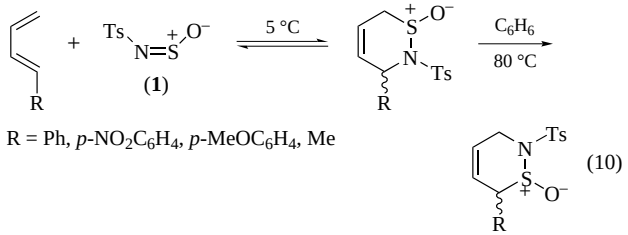


(8)

Diels–Alder Reactions. *N*-Sulfinyl compound (**1**) is an effective dienophile in the regioselective [4 + 2] cycloaddition of unsymmetrical dienes.[1b,10,11] For example, 2-substituted dienes were found to yield only 5-substituted dihydrothiazine oxides (eq 9). The cycloaddition of (**1**) with simple 1-substituted 1,3-dienes is often dependent on the reaction temperature. At low temperatures, 3-substituted dihydrothiazine oxides are usually formed as kinetic products, but at higher temperatures the more stable 6-substituted heterocycles are produced (eq 10).[12]

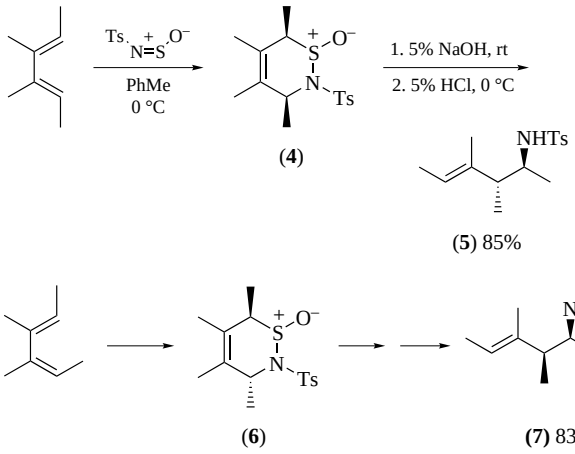


(9)



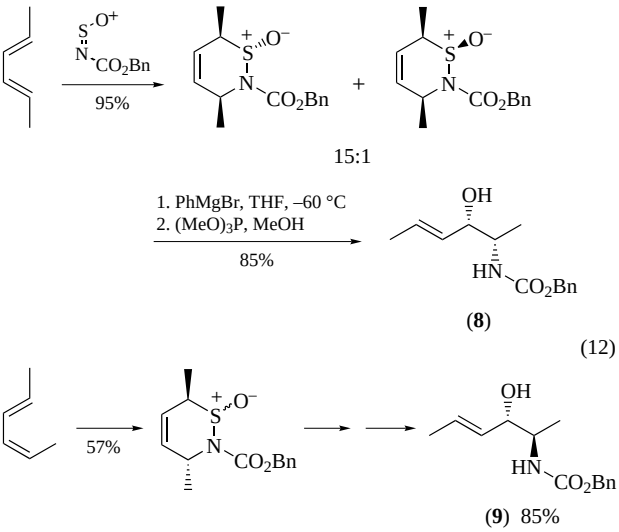
(10)

The dihydrothiazine oxides derived from this hetero Diels–Alder process are valuable synthetic intermediates in constructing homoallylic amines and vicinal amino alcohols in a stereorational manner.[11] For instance, in a system involving the diastereoselective synthesis of unsaturated acyclic amines, (**1**) was combined with (*E*,*E*)-tetramethylbutadiene to give cycloadduct (**4**), whereupon hydrolysis and retro-ene loss of SO_2 via a rigid chair-like transition state afforded exclusively the (*E*)-homoallylic amine derivative (**5**) (eq 11).[11,13] Similarly, (*E*,*Z*)-tetramethylbutadiene produced 3,6-dihydrothiazine oxide (**6**), which was hydrolyzed to give (*E*)-homoallylic sulfonamide (**7**).



(11)

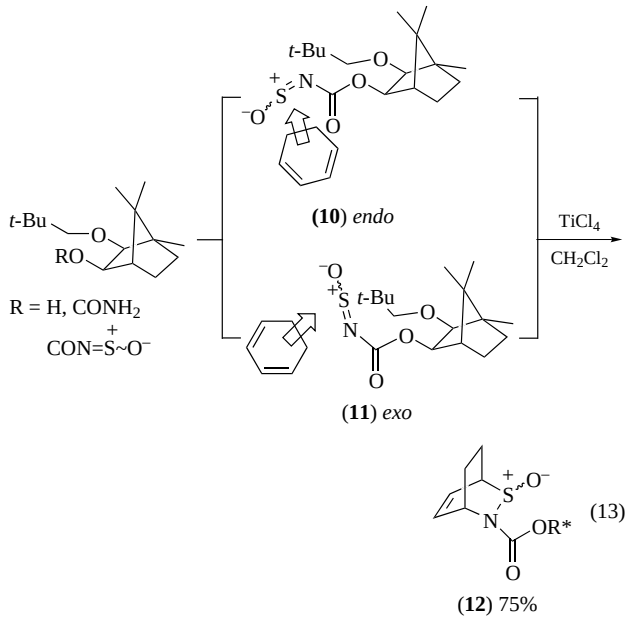
In a related system involving the diastereoselective synthesis of unsaturated vicinal amino alcohols, the Diels–Alder cycloaddition of (*E*,*E*)-hexadiene with benzyl *N*-sulfinylcarbamate.[14] gave a 15:1 mixture of epimeric adducts (eq 12). Ring opening of these cycloadducts with phenylmagnesium bromide, followed by the [2,3]-sigmatropic rearrangement of the intermediate allylic sulfoxide in the presence of trimethyl phosphite, yielded the (*E*)-*threo* vicinal amino alcohol derivative (**8**) Similarly, (*E*,*Z*)-hexadiene underwent the *N*-sulfinyl Diels–Alder reaction and subsequent steps to give the (*E*)-*erythro* hydroxy carbamate (**9**) exclusively.



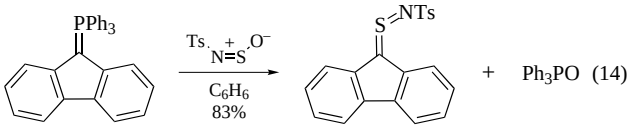
(12)

The chiral *N*-sulfinyl carbamate prepared from (+)-camphor (eq 13)[15] displayed high enantioselectivity in the titanium(IV) chloride catalyzed [4 + 2] cycloaddition with 1,3-cyclohexadiene, affording only one cycloadduct. The stereochemistry of compound (**12**) can be rationalized by a cycloaddition occurring through either conformer (**10**) via an *endo* transition state or

conformer (**11**) by an *exo* transition state. High levels of asymmetric induction have also been reported in the cycloaddition reactions of *N*-sulfinylcarbamates derived from the chiral auxiliary 8-phenylmenthol.[16]



Wittig-type Reaction. TsNSO undergoes an interesting Wittig-type reaction with triphenylphosphonium fluorenylide to afford thione *S*-imides in good yields (eq 14).[17]



1. (a) Bussas, R.; Kresze, G.; Munsterer, H.; Schwobel, A., *Sulfur Rep.* **1983**, *2*, 215. (b) Boger, D. L.; Weinreb, S. M. In *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic: Orlando, 1987; Chapter 1. (c) Schubart, R., *Methoden Org. Chem. (Houben-Weyl)* **1985**, *E11*, 122.
2. (a) Hori, T.; Singer, S. P.; Sharpless, K. B., *J. Org. Chem.* **1978**, *43*, 1456. (b) Kresze, G.; Wucherpfennig, W., *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 149.
3. Kim, Y. H.; Shin, J. M., *Tetrahedron Lett.* **1985**, *26*, 3821.
4. (a) Albrecht, R.; Kresze, G.; Mlakar, B., *Chem. Ber.* **1964**, *97*, 483. (b) Albrecht, R.; Kresze, G., *Chem. Ber.* **1965**, *98*, 1431. (c) Pozdnyakova, T. M.; Sergeyev, N. M.; Gorodetskaya, N. I.; Zefirov, N. S., *Int. J. Sulfur Chem., Part B* **1972**, *2*, 109.
5. (a) Sisko, J.; Weinreb, S. M., *Tetrahedron Lett.* **1989**, *30*, 3037. (b) Sisko, J.; Weinreb, S. M., *J. Org. Chem.* **1990**, *55*, 393. (c) Ralbovsky, J. L.; Kinsella, M. A.; Sisko, J.; Weinreb, S. M., *Synth. Commun.* **1990**, *20*, 573. (d) Alexander, M. D.; Anderson, R. E.; Sisko, J.; Weinreb, S. M., *J. Org. Chem.* **1990**, *55*, 2563. It has also been shown that reductive carbamation of simple aldehydes can be effected in a similar procedure utilizing *N*-sulfinylbenzyl carbamate.
6. McIntosh, M. C.; Weinreb, S. M., *J. Org. Chem.* **1993**, *58*, 4823.
7. Melnick, M. J.; Freyer, A. J.; Weinreb, S. M., *Tetrahedron Lett.* **1988**, *29*, 3891.
8. (a) Kresze, G.; Bussas, R., *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 732 and 737. (b) Bussas, R.; Munsterer, H.; Kresze, G., *J. Org. Chem.* **1983**, *48*, 2828.
9. For uses of related *N*-sulfinyl compounds such as *N*-sulfinyl-(*β*-(trimethylsilyl)ethyl)sulfonamide and *N*-sulfinyl-(*p*-methylphenyl)-methanesulfonamide see: Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M., *J. Am. Chem. Soc.* **1990**, *112*, 3475 and Ref. 5a.
10. Kresze, G. In *1,4-Cycloaddition Reactions, the Diels–Alder Reaction in Heterocyclic Synthesis*, Hamer, J., Ed.; Academic: New York, 1967; p 453.
11. Weinreb, S. M., *Acc. Chem. Res.* **1988**, *21*, 313.
12. The thermal Diels–Alder reaction of *N*-alkyl-*N*-sulfinyl dienophiles with 1,3-dienes fails except in the presence of a Lewis acid catalyst or under high pressure. See: Bell, S. I.; Weinreb, S. M., *Tetrahedron Lett.* **1988**, *29*, 4233.
13. Garigipati, R. S.; Morton, J. A.; Weinreb, S. M., *Tetrahedron Lett.* **1983**, *24*, 987.
14. This *N*-sulfinyl compound was prepared from benzyl carbamate with thionyl chloride and pyridine. Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M., *J. Am. Chem. Soc.* **1984**, *106*, 7861.
15. Prepared from the corresponding carbamate, thionyl chloride, and pyridine. Remiszewski, S. W.; Yang, J.; Weinreb, S. M., *Tetrahedron Lett.* **1986**, *27*, 1853.
16. Whitesell, J. K.; James, D. Carpenter, J. F., *J. Chem. Soc., Chem. Commun.* **1985**, 1449.
17. Saito, T.; Motoki, S., *J. Org. Chem.* **1977**, *42*, 3922.

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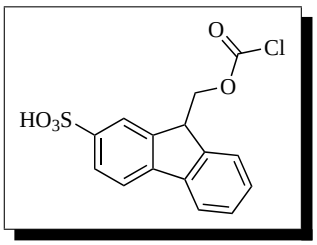
9-(2-Sulfo)fluorenylmethoxycarbonyl Chloride



[67827-06-9] $C_{15}H_{11}ClO_5S$ (MW 338.76)

InChI = 1/C15H11ClO5S/c16-15(17)21-8-14-11-4-2-1-3-10(11)12-6-5-9(7-13(12)14)22(18,19)20/h1-7,14H,8H2,(H,18,19,20)/f/h18H

InChIKey = RDNRMPYXJPJOLS-GPQMBLKYCQ

(base-labile, water-soluble protecting group for amines; chemoselective tag used in peptide synthesis for the purification of large peptides[1])

Alternate Names: Sulfmoc-Cl; 9-fluorenylmethoxycarbonyl-SO_3H chloride; FMS-Cl.

Physical Data: mp 138–140 °C.

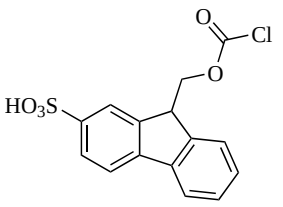
Solubility: soluble in most organic solvents except alkanes. Sulfmoc analogs are soluble in water, but Sulfmoc-Cl itself reacts very quickly with this solvent.

Form Supplied in: Sulfmoc-Cl (white solid) is not commercially available.

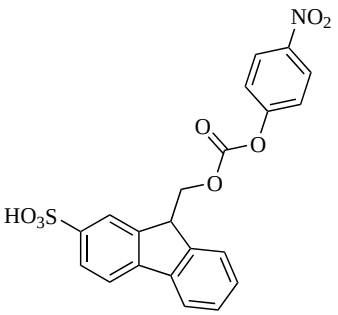
Handling, Storage, and Precautions: Sulfmoc-Cl is an acid chloride and should therefore be protected from moisture. Sulfmoc-Cl has been reported to be hygroscopic. Bottles may develop pressure as the reagent evolves CO_2 upon degradation. Closely related Fmoc-Cl has been reported to be lachrymator and very harmful if swallowed, inhaled, or absorbed through skin, and similar handling precautions should be taken if working with Sulfmoc-Cl (use a fumehood).

Preparation and Purification of *N*-Terminal Sulfmoc Protected Peptides. Sulfmoc-Cl (**1**),[2] Sulfmoc-ONp (**2**),[2] and Sulfmoc-OSu (**3**)[3] were produced in very good yields by selective electrophilic sulfonation ($ClSO_3H$) of the more electron-rich position of corresponding Fmoc derivatives. Chloroformates (**1**) and active carbonates (**2** and **3**) are stable under these conditions.

Sulfmoc-Cl has been used to protect the free amine of the growing peptide chain in the last step of a solid-phase synthesis. Sulfmoc carbamates exhibit good stability to strong acidic conditions and therefore are not affected by the peptide-resin cleavage with HBr/AcOH or HF. However, because of the electron-withdrawing sulfonic acid substituent, deprotection can be accomplished under milder basic conditions than are needed for the related Fmoc derivatives. The sulfonic acid group (pKa ≈ -1.3) is fully ionized in 1 M aqueous formic acid, while α- and ω-carboxyl groups of amino acid residues are protonated at this pH. The Sulfmoc group can therefore serve as a probe such that ion-exchange chromatography can be used to obtain the desired peptide product free of the truncated peptides. In an alternative more simple purification procedure, the Sulfmoc peptide may be absorbed on a quaternary ammonium resin column and the Sulfmoc group can be cleaved on the resin by washing with aq NEt_3. The desired free peptide is then eluted with 1 M formic acid.[2]



1



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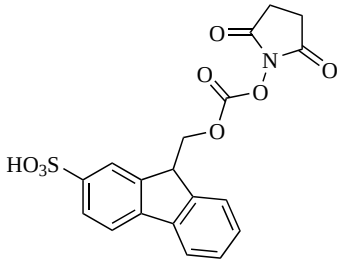

3

Water-soluble Long-acting Prodrug Approach.[3,4] A $(Sulfmoc)_3$-insulin conjugate has been designed as a prolonged-acting preparation of insulin.[3] This prodrug escapes receptor-mediated endocytosis and degradation, and undergoes slow spontaneous regeneration of insulin at physiological pH. However, many aromatic and polyaromatic hydrocarbons are carcinogenic, and the fate of released 2-sulfodibenzofulvene should therefore be elucidated before any clinical development of Sulfmoc-drug conjugates.

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1. Mascagni, P., In *Fmoc Solid Phase Peptide Synthesis: A Practical Approach*; Chan, W. C.; White, P. D., Eds; Oxford University Press: Oxford, 2000, p. 265.
2. Merrifield, R. B.; Bach, A. E., *J. Org. Chem.* **1978**, *43*, 4808.
3. Gershonov, E.; Goldwaser, I.; Fridkin, M.; Shechter, Y., *J. Med. Chem.* **2000**, *43*, 2530.
4. Shechter, Y.; Preciado-Patt, L.; Schreiber, G.; Fridkin, M., *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 1212.

Didier Stien
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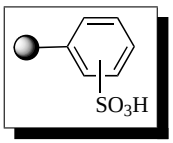
Sulfonic Acid, Polymer-supported



[39389-20-3]
[63182-08-1]
[12612-37-2]

(reagent used in the synthesis of substituted amides, acids, esters, substituted aromatic derivatives, acetals, ketals, methyl ketones; used in hydrolysis of oximes, semicarbazones, hydrazones; reduction of oximes; aldol condensation; used as an ion-exchange resin for purification of amines)

Alternative Names: Amberlyst 15,[1] Amberlite IR-120, and Dowex 50.

Physical Data: the title reagent appears as gray beads.

Solubility: insoluble in organic solvents.

Form Supplied in: Amberlyst 15 (20–60 mesh beads), Amberlite IR-120 (8% cross-linked beads), and Dowex 50 (2% cross-linked mesh (dry) 50–100 mesh beads).

Purification: these polymeric acids can be regenerated by the addition of HCl.

Handling, Storage, and Precautions: (a) precautions for safe handing and use: dry ion-exchange resins can expand on the addition of solvent, which may cause the column to shatter. The maximum operating temperature recommended is 120 °C. Nitric acid and other strong oxidizing materials can cause explosive reactions when mixed with ion-exchange resins.[2] (b) Reactivity data: heat sensitive, avoid temperatures over 220 °C. Forms explosive mixtures with acids and strong oxidizing agents. Hazardous decomposition products formed are

toxic fumes of carbon monoxide, carbon dioxide, and sulfur oxides. Styrene monomer and divinylbenzene may also be formed. (c) Fire and explosion hazard data: this material, like most materials in powder form, is capable of creating a dust explosion. Emits toxic fumes under fire conditions. Avoid contact with skin and eyes.[3]

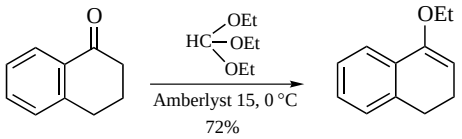
Disposal: beads should be neutralized and disposed by mixing the material with a combustible solvent and burning in a chemical incinerator equipped with an afterburner and scrubber.

Original Commentary

Steven V. Ley & A. Horvath
University of Cambridge, Cambridge, UK

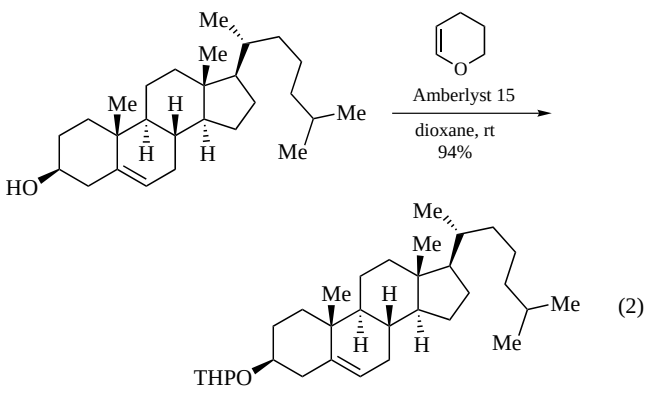
General. Polymer-supported sulfonic acids are reliable catalysts for many acid-mediated reactions.[4] Macroreticular polystyrene-based resins such as Amberlyst 15 are preferentially used in organic solvents, whereas Dowex resins work better in aqueous solutions. All resins are insoluble and can be separated from reactions by simple filtration.

Formation of Acetals and Ketals. The protection of carbonyl groups as acetals or ketals is a necessary requirement for the manipulation of many multifunctional molecules. Amberlyst 15[5–7] and Dowex 50[8] are excellent acidic catalysts for such transformations. When triethyl orthoformate[9] (eq 1) is used, enol ether formation from α,β-unsaturated carbonyls can also occur.



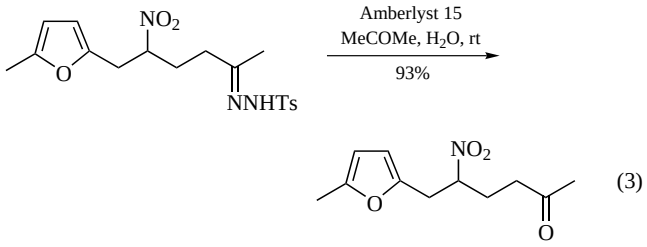
(1)

In the presence of polymer-supported (PS) SO_3H resins, *t*-butyl ethers[10] and tetrahydropyranyl ethers[11] of alcohols and phenols are formed. Elimination by-products that are formed during the protection of secondary and tertiary alcohols (eq 2) can be avoided using PS-SO_3H. Additionally, selective tetrahydropyran protection of primary and secondary symmetrical diols can be undertaken to yield monoprotected products.[12] In the presence of water, Dowex 50W and Amberlite IR-120 give higher yields of monoethers than Amberlyst 15.



(2)

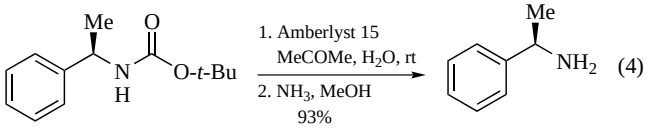
Regeneration of Carbonyl and Amino Groups. Excellent yields are obtained in the formation of carbonyl compounds from acetals, ketals,[13,14] tosyl hydrazones (eq 3), oximes, 2,4-dinitrophenylhydrazones, and semicarbazones[15] when reactions are carried out in an acetone/water mixture.



(3)

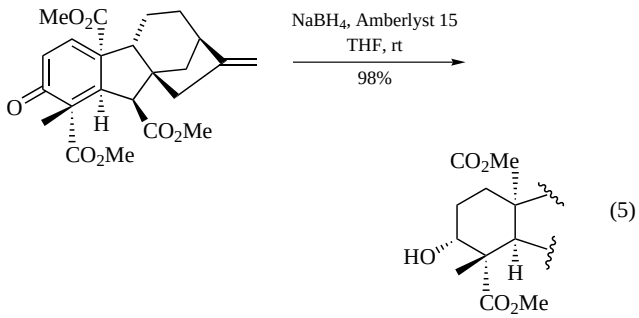
Thioacetals of ketones and activated aldehydes can be removed using a combination of paraformaldehyde and Amberlyst 15 in aqueous acetone.[16] Unsubstituted amides and carboxylic acid hydrazides can be selectively converted into the corresponding acids and esters using Amberlyst 15 in refluxing water, MeOH, or EtOH.[1] This procedure permits selective hydrolysis in the presence of esters, substituted amides, and nitriles.

Both primary and secondary Boc-protected aliphatic amines can be purified and deprotected efficiently by treatment with Amberlyst 15 (catch-and-release technique) without causing any racemization (eq 4).[17] Amberlite IR-120 resin can be used for deprotection of *N*-*p*-toluenesulfinyl-protected amines.[18]



(4)

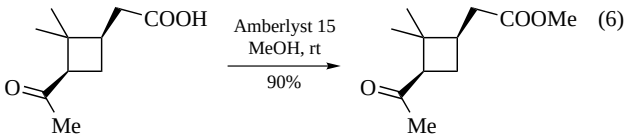
Reduction. Unreactive and hindered ketones are reduced within a few minutes using a combination of sodium borohydride and Amberlyst 15 in THF.[19] Under the same conditions, cyclic ketones are reduced with a high level of stereoselectivity in the presence of ketals, silyl ethers, acetals, allylic acetals, lactones, esters, and halides (eq 5). The reduction of oximes and subsequent cleavage of the N–O bond to yield amines can be performed using Amberlyst 15 with **LiCl–$NaBH_4$** complex in THF.[20] In contrast to the **$NiCl_2$/$NaBH_4$** system, this reduction gives allylic amines from conjugated oximes.



(5)

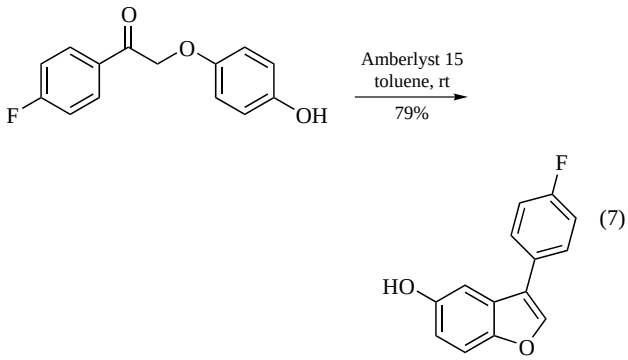
Ester Formation. Amberlyst 15 has also been employed in the methyl esterification[21] of chiral carboxylic acids (eq 6).[22] In

esterification reactions of carboxylic acids with olefins,[23] Amberlyst 15 is used as a superior catalyst to Amberlyst XN-1010. Comparable results have been observed between microwave-assisted and classically heated heterogeneous reactions using isopentyl alcohol and acetic acid.[2]



(6)

Dehydration and Cyclization. Amberlyst 15 has been used in the cyclodehydration of pentane-1,5-diol to tetrahydropyran[24] and in the synthesis of a library of substituted benzofurans (eq 7).[25] In a similar procedure, 2,5-dimethylfuran has been formed in excellent yield by distillation from hexane-2,5-dione (eq 8).[24]



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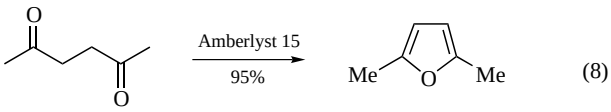
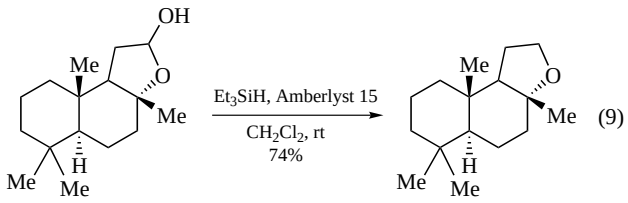


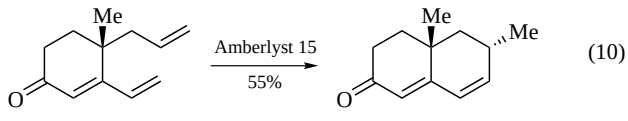
(8)

Dehydration and reduction of lactols into the corresponding cyclic ethers can be carried out in high yields using Amberlyst 15 and triethylsilane (eq 9).[26]

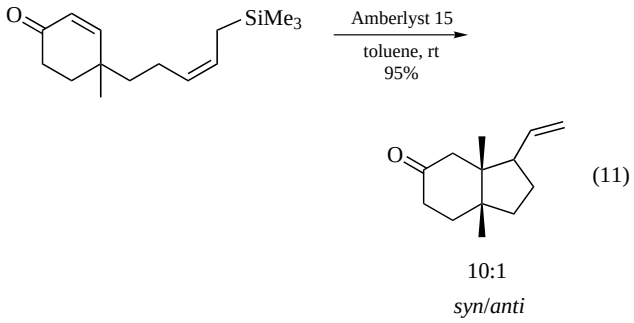


(9)

Amberlyst 15 has been employed in cation–olefin cyclization from trienones in the formation of six- (eq 10) and seven-membered rings.[27] Fused bicyclic structures have also been synthesized by intramolecular additions of allylic silanes to cyclic enones (eq 11).[28]



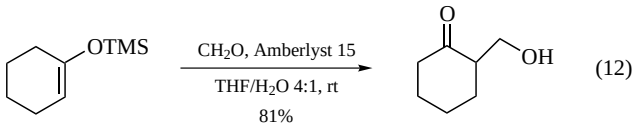
(10)



(11)

Miscellaneous. Sodium bromide or sodium iodide can be used with Amberlyst 15 to effect regioselective ring-opening reactions of substituted aziridine-2-carboxylates to α-halo-β-amino esters.[29] 1,3-Dicarbonyl compounds can be brominated using potassium bromate/potassium bromide in the presence of Dowex resin.[30] Amberlyst 15-bound sulfonic acid groups are oxidized by aqueous hydrogen peroxide at 70 °C and the peracid that is formed has been used in Baeyer–Villiger oxidation of cyclopentanone.[31]

Trivalent lanthanides are used with Amberlyst 15 in a variety of organic reactions requiring hard Lewis acid catalysts.[7] These conditions can be used for aza-Diels–Alder reactions, transacetalizations,[32] ring-opening reactions of oxiranes with nucleophiles, and as a promotor in glycosylations of glucosyl fluorides in methanol. The ytterbium-mediated Mukaiyama aldol reaction of a silyl enol ether with formaldehyde can be conducted in aqueous THF solution with paraformaldehyde (eq 12). Lanthanide(III) catalysts supported on Amberlyst 15 and Amberlyst XN-1010 are more effective catalysts compared to other exchange resins.



(12)

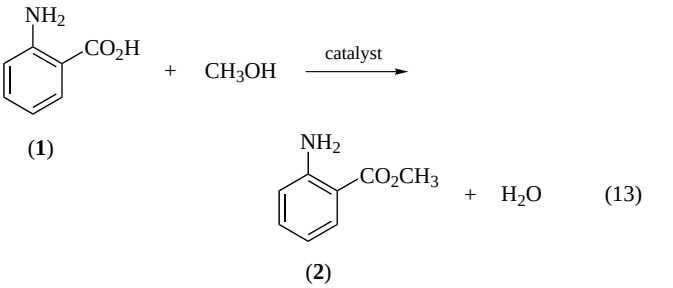
PS-SO_3H resins can be used as scavengers for removal of cations or basic impurities from reaction mixtures.[33,34] The sulfonic acid resins can also be employed in the purification of amines by 'catch-and-release' methodology. The amine is covalently bound to the resin, can be separated from impurities by filtration, and is released by treatment with an ammonia solution.[17,18,35,36]

First Update

Jason Eames
Queen Mary University of London, London, UK

Synthesis of Substituted Amides, Carboxylic Acids, and Esters Using Polymeric Supported Sulfonic Acid. The use of strong acids as an acid catalyst for the formation of esters derived from carboxylic acids is well known. The use of polymeric acids is less documented; however, they appear to have a significant advantage over their related nonpolymeric supported acids, as they can easily be removed at the end of a reaction sequence by simple filtration.[4,37]

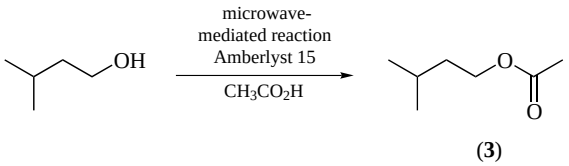
In this area, Yadav and Krishnan[38] have investigated the use of polymeric supported acids as catalysts in the large-scale synthesis of a known perfumery and flavoring agent, methyl anthranilate (**2**), derived from the corresponding carboxylic acid **1** and an excess of methanol (eq 13). They have shown that Amberlyst 15 was the most efficient polymeric supported acid screened and was far superior to related polymeric acids such as Indion-130, Bayer K-24, Amberlyst 18, and Dowex M-32.



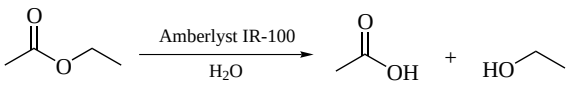
(13)

Efficiency of catalyst:
Amberlyst 15 > Indion-130 > Bayer K-24 > Amberlyst 18 > Dowex M-32

Amberlyst 15 has also found use as an efficient acid catalyst in the synthesis of low molecular weight esters such as 3-methylbutyl acetate (**3**) by using acetic acid as the carboxylic acid component (eq 14).[2] This reaction was performed under microwave-mediated conditions, which illustrates the thermal stability of Amberlyst 15 under these reaction conditions. A related sulfonic acid resin, Amberlite IR-100, has been used as an acid catalyst for the hydrolysis of ethyl acetate to give acetic acid and ethanol by conducting the reaction in water (eq 15).[39] It is interesting to note that the use of a less acidic polymeric supported carboxylic acid resin (Wofatit C) was at least 20 times less efficient than Amberlite IR-100 itself.

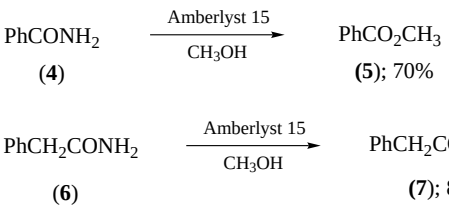


(14)



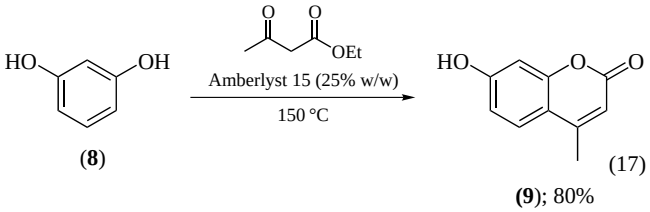
(15)

It has also been shown that substituted methyl esters, such as **5** and **7**, can be synthesized directly by the addition of methanol to the amides **4** and **6**, respectively, by using a large excess of Amberlyst 15 (1500% w/w) (eq 16).[1] This reaction appears to proceed smoothly, allowing efficient conversion of the amide to the required ester in good to high yield.



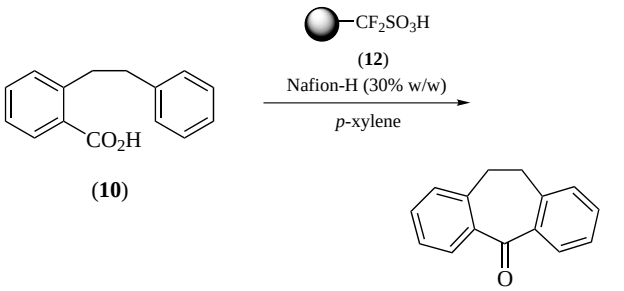
(16)

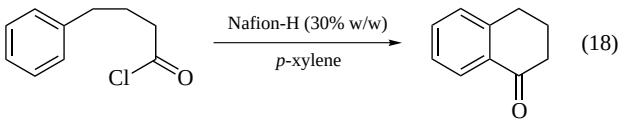
Amberlyst 15 has also been used in the von Pechmann coupling of ethyl acetoacetate to a variety of substituted phenols, such as resorcinol (**8**), to give substituted hydroxycoumarins such as **9** (eq 17).[40] This reaction appears to occur efficiently with a substoichiometric amount of Amberlyst 15 (25% w/w).



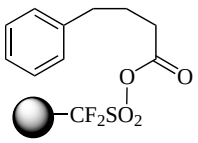
(17)

Synthesis of Substituted Aromatic Derivatives Using Polymeric Supported Sulfonic Acid. Yamato[41] has investigated the synthesis of dibenzocycloheptanone (**11**) by refluxing diphenylethane-2-carboxylic acid (**10**) in *p*-xylene using a related polymeric supported sulfonic acid resin, Nafion-H (**12**) (30% w/w) (eq 18). It is particularly interesting to note that this cyclization has a temperature threshold; that is, above 138 °C the cyclization occurs efficiently, whereas below this temperature only starting material was recovered. This methodology has been extended toward the synthesis of aryl ketones, such as tetralone (**14**), by refluxing acid chloride (**13**) in *p*-xylene with Nafion-H (30% w/w) (eq 18). This reaction is thought to proceed via derivatization of the polymeric supported sulfonic acid resin itself to give an activated sulfonic anhydride (**15**).



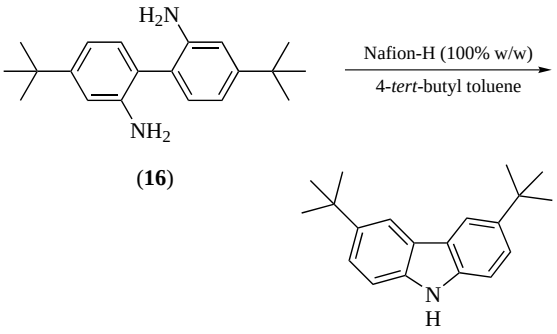


(18)



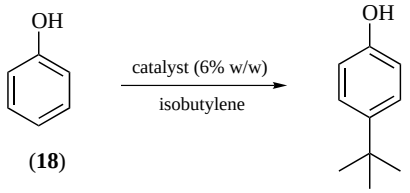
Yamato has also extended this carbocyclic cyclization reaction to the synthesis of substituted carbazoles such as **17** by refluxing a solution of 2,2′-diaminobiphenyls (**16**) in 4-*tert*-butyl toluene with a stoichiometric amount of Nafion-H (100% w/w).[42] This cyclization appears to be significantly slower than the related cyclization

that gave dibenzocycloheptanone (**11**) since a higher reaction temperature was required to force the reaction to completion (eq 19).



(**16**) (**17**); 88% (19)

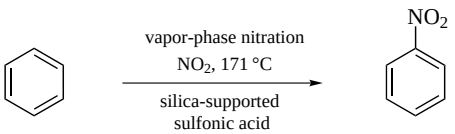
Loev and Massengale[43] have investigated the electrophilic mediated addition of isobutylene to phenol (**18**) to give *p-tert*-butyl phenol (**19**) using either Amberlite IR-120 or Dowex 50 as an acid catalyst (6% w/w) (eq 20). They found that Amberlite IR-120 was the more efficient acid catalyst for this process.



(**18**) (**19**) (20)

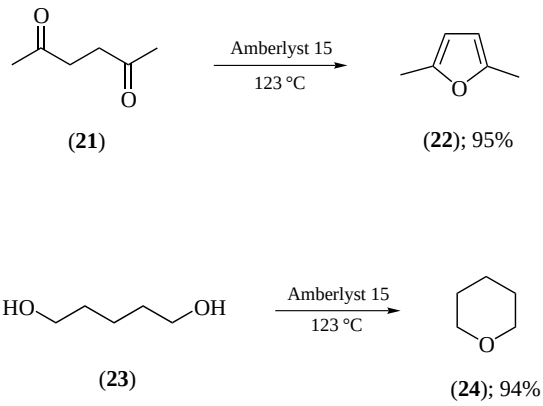
Catalyst	Yield (%)
Amberlite IR-120	57
Dowex 50	49

The physical nature of the polymer that supports the sulfonic acid functionality appears to play a minor role in these reactions. Suzuki[44] has reported the use of a silica-supported sulfonic acid as an efficient acid catalyst for the vapor-phase nitration of benzene with gaseous NO_2 to give nitrobenzene (**20**) (eq 21). This nitration process is particularly efficient as it gives nitrobenzene in 93% yield.



(**20**); 93% (21)

Synthesis of Acetals, Ketals, and Enol Ethers Using Polymeric Supported Sulfonic Acid. Amberlyst 15 has been used as an acid catalyst in the dehydration of 1,4-diketone (**21**) to give the 2,5-disubstituted furan (**22**) (eq 22).[45] This dehydration procedure required only a substoichiometric amount of Amberlyst 15 (1% w/w) to give the required furan (**22**) in near quantitative yield. This dehydration process has been extended toward the synthesis of tetrahydropyrans such as **24** by dehydration of diol **23** (eq 22).

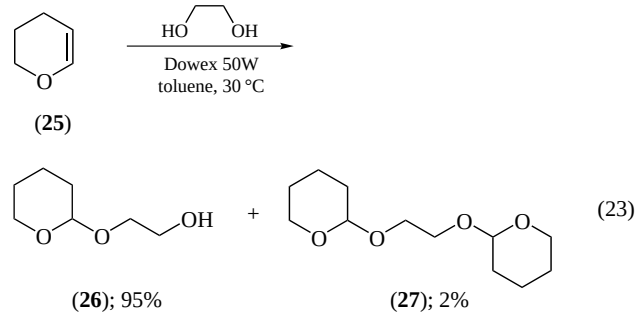


(**21**) (**22**); 95%

(**23**) (**24**); 94% (22)

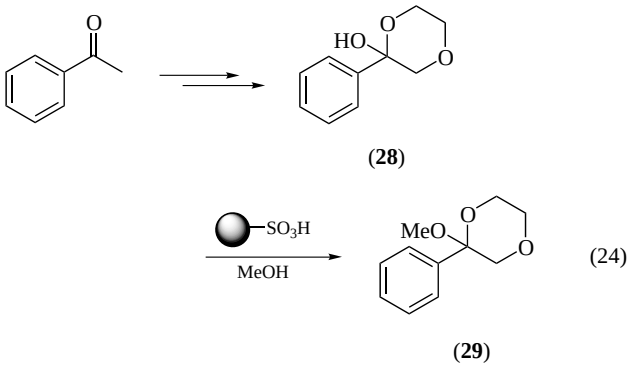
Dowex 50W has also been used as an acid catalyst in the formation of substituted acetals (eq 23).[12] Nishiguchi has shown that the optimum amount of Dowex 50W needed for an efficient synthesis of monoacetal (**26**) was 0.1 g per mmol of ethylene glycol.[12] This reaction is particularly impressive since it minimized the competitive formation of the diacetal (**27**).

It was also found that the type of sulfonic acid resin used was particularly important for the outcome of the reaction; dry Amberlyst 15 gave very little product (5%), whereas wet Amberlyst 15 gave significantly more (50%). However, using a related resin, Amberlyst IR-118 (H), the required acetal (**26**) could be obtained in excellent yield (95%). By comparison, a nonpolymer sulfonic acid such as camphor sulfonic acid (CSA) gave only a 17% yield of the product (eq 23).[12]



(**25**) (**26**); 95% (**27**); 2% (23)

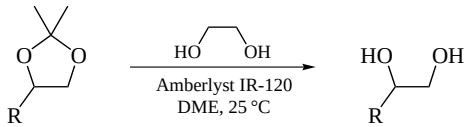
Ley[8] has reported the formation of unsymmetrical ketals such as **29** using Dowex 50W as an acid catalyst. Addition of Dowex 50W to a stirred solution of hemiketal (**28**) in methanol gave the ketal **29** in high yield (eq 24). To ensure that the reaction went to completion, around 2 g of Dowex 50W per mmol of **28** was required. The clear advantage of this approach was that the Dowex 50W resin could simply be removed by filtration to give the corresponding ketal, such as **29**, which was shown to be of high purity by ^1H and ^{13}C NMR spectroscopic analyses and LC-MS.



(**28**)

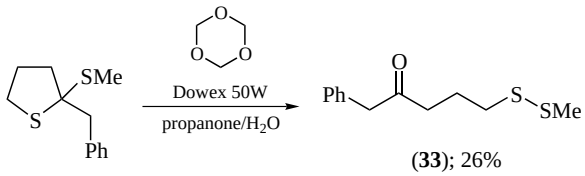
(**29**) (24)

Tius[46] has reported the reverse process wherein Amberlyst IR-120 was used as an acid catalyst to deprotect propanone-based ketals such as **30** through transketalization with ethylene glycol to liberate the required diol **31** (eq 25). This equilibration appears to work efficiently with Amberlyst IR-120 resin (225% w/w) giving the substituted diol **31** in 80% yield.



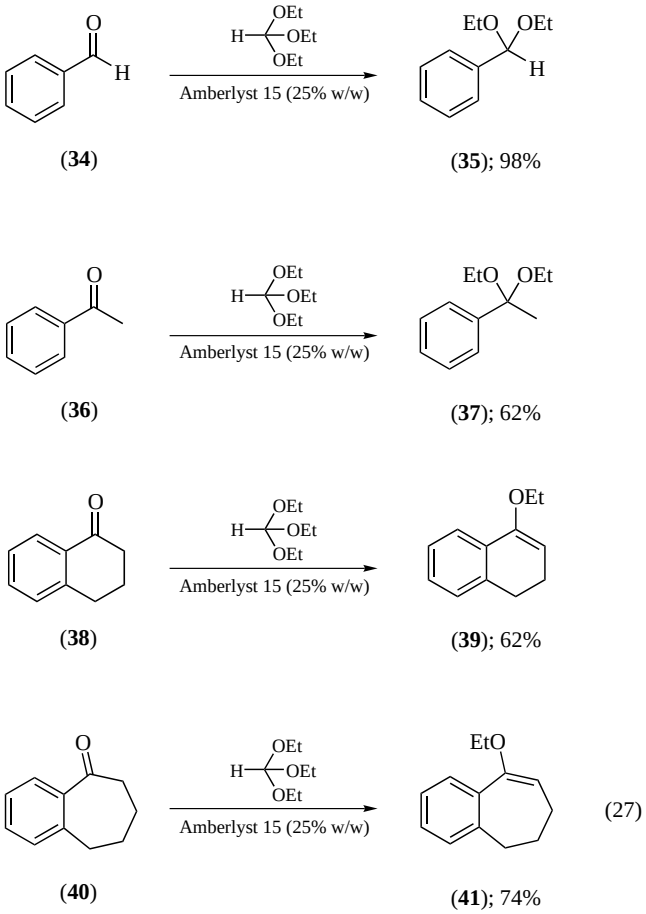
(**30**) (**31**); 80% (25)

Dithioketals such as **32** have also been deprotected to give substituted ketones, such as **33**, using a mixture of Dowex 50W (1000% w/w) in propanone and water (eq 26).[47] However, these reactions proceeded in low to moderate yield, presumably due to the reduced basicity of the dithioketal motif compared to that of ketals.



(**32**) (**33**); 26% (26)

Patwardhan and Dev[9] investigated the substitution pattern within a series of phenyl alkyl ketones (**34**, **36**, **38**, and **40**) in an attempt to probe the competition between acetal, ketal, and enol ether formation (eq 27). They showed that acyclic aldehydes and ketones such as benzaldehyde (**34**) and acetophenone (**36**) prefer acetal (**35**) and ketal (**37**) formation, respectively, whereas cyclic ketones such as tetralone (**38**) and benzosuberone (**40**) favor formation of the corresponding enol ethers **39** and **41** Presumably, this process is governed in part by the stability of the carbon–carbon double bond of the enol ether; that is, the more substituted is the double bond, the more preferred is the enol ether formation.



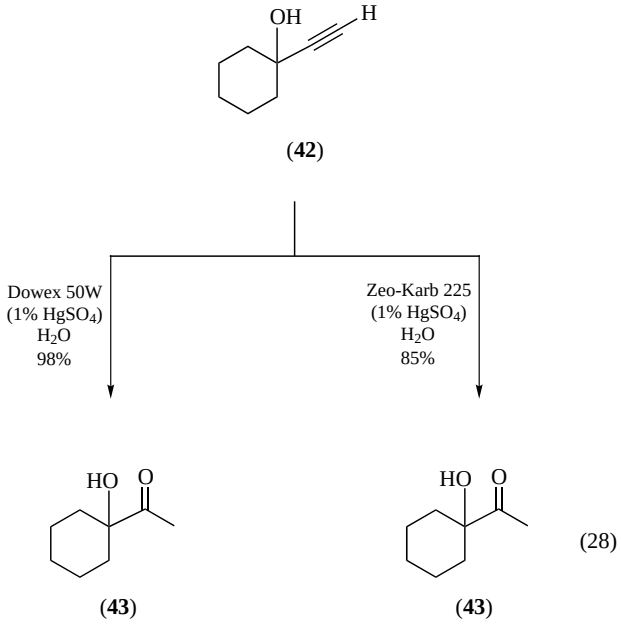
(**34**) (**35**); 98%

(**36**) (**37**); 62%

(**38**) (**39**); 62%

(**40**) (**41**); 74% (27)

Synthesis of Methyl Ketones Using Polymeric Supported Sulfonic Acid. Newman[48] has shown that Dowex 50W (impregnated with 1% $HgSO_4$) was an efficient catalyst for the hydration of alkynes to the corresponding methyl ketones, such as in the transformation of **42** to **43** in 98% yield (eq 28). This optimized process required 20% w/w of Dowex 50W to allow the reaction to proceed to completion. This work was later extended[49] through

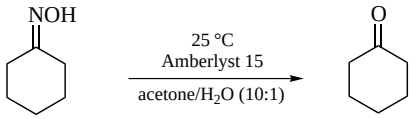


(**42**)

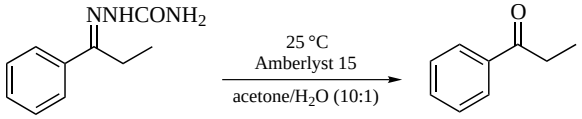
(**43**) (**43**) (28)

the use of a polystyrene sulfonic acid based resin, Zeo-Karb 225, impregnated with 1% $HgSO_4$ (25% w/w). However, the use of this particular polymeric supported sulfonic acid resin lowered the overall yield to 85% (eq 28).

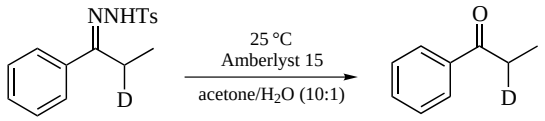
Hydrolysis of Oximes, Semicarbazones, and *N*-Tosyl Hydrazones Using Polymeric Supported Sulfonic Acid. Ballini[50] has used Amberlyst 15 as an acid catalyst for the deprotection of oximes (**44**) and semicarbazones (**46**) to give the parent ketones **45** and **47**, respectively (eq 29). These reactions required around 2 g of Amberlyst 15 per 0.01 mmol of substrate. However, the procedure does appear to be particularly mild, allowing the selective hydrolysis of an *N*-tosyl hydrazone to occur without the loss of the deuterium label adjacent to the carbonyl group (eq 29).



(**44**) (**45**); 92%



(**46**) (**47**); 90%

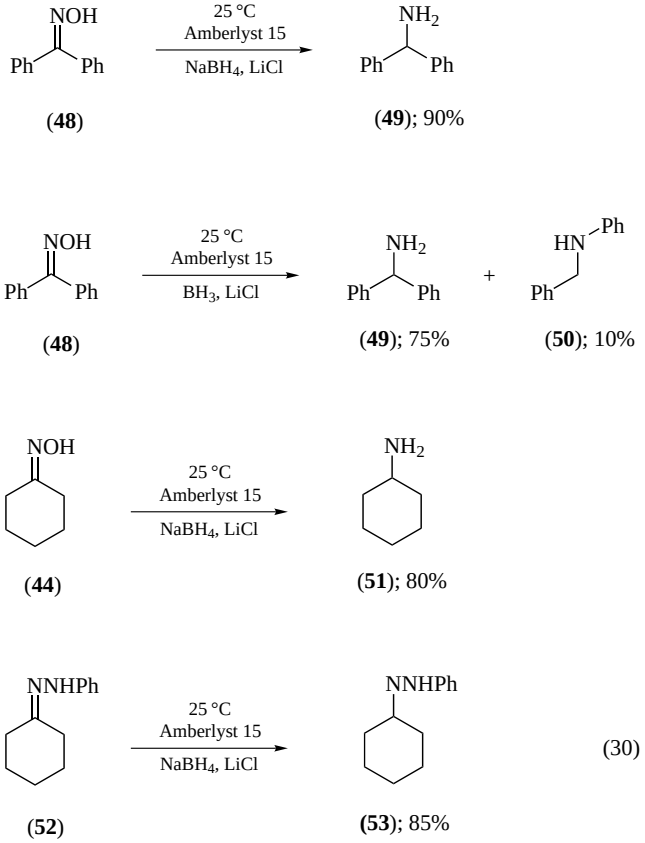


(29)

86%

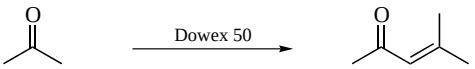
Reduction of Oximes Mediated by Polymeric Supported Sulfonic Acid. Under related conditions, Sandhu[20] has shown that oximes such as **48** can efficiently be reduced using Amberlyst 15 and lithium chloride-mediated sodium borohydride reduction to the corresponding primary amine **49** in high yield (eq 30). This process appears to be particularly selective in favoring reduction. When sodium borohydride was replaced by borane, the yield of the required amine **49** was reduced to 75%. The remaining product **50** was derived from an in situ Beckmann rearrangement. It is worth noting that this reaction did not occur when a large excess of sodium borohydride (in methanol) was used, whereas a change of counterion from sodium to lithium (borohydride) improved the yield of **49** to 30%. The presence of Amberlyst 15 (1.2 g per 1 mmol of substrate) is very important for the outcome of this reduction process, in particular in its ability to increase the yield. This reaction has been extended toward the synthesis of substituted amines such as **51** (derived from oxime **44**) and hydrazine (**53**) derived from hydrazone (**52**).

Aldol Condensation Using Polymeric Supported Sulfonic Acid. In the absence of solvent, propanone (**54**) has been shown



(30)

to undergo an aldol condensation to give mesityl oxide (**55**) in 80% yield by simply passing the refluxing propanone vapor over a Dowex 50W column (eq 31).[51] This procedure is particularly efficient since mesityl oxide **55** can be continually collected in the original reaction vessel; consequently, it can be performed on a reasonably large scale (up to 1.2 kg).

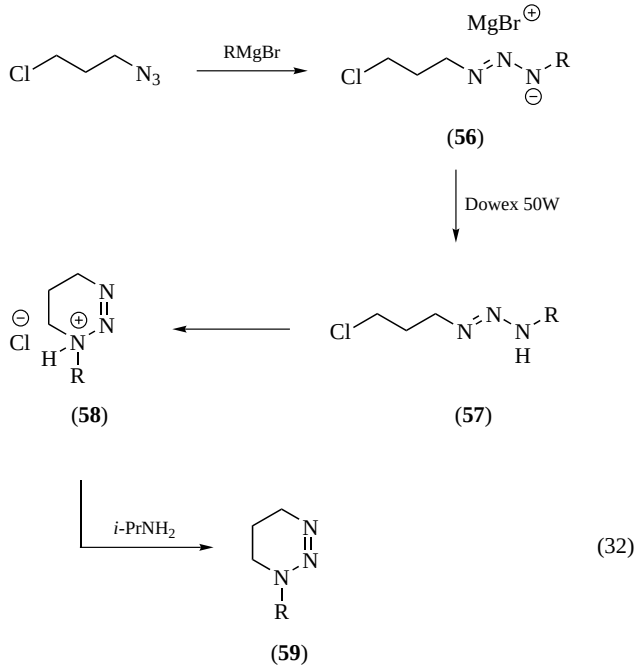


(31)

(**54**) (**55**); 80%

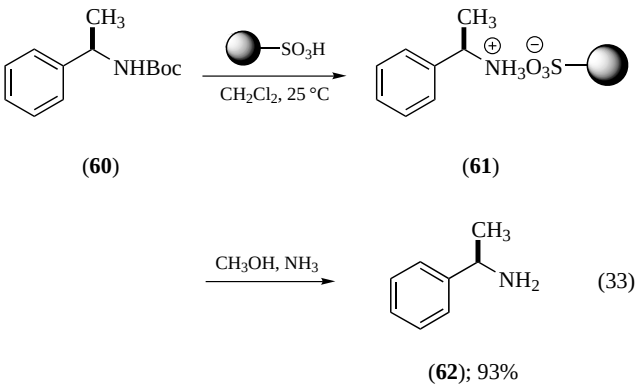
Direct Protonation Using Polymeric Supported Sulfonic Acid. The use of Dowex 50W as a simple Brønsted acid in organic synthesis is less documented. In an attempt to address this imbalance, Farnsworth[52] has used Dowex 50W (200% w/w) as a polymeric base scavenger to remove an excess of Grignard reagent (RMgBr) through protonation. The resin also serves to protonate the intermediate magnesium triazide (**56**) to give the linear triazene (**57**). This triazene spontaneously cyclizes by the loss of a chloride anion to give the protonated triazene (**58**), which, on basification, afforded the cyclic triazene (**59**) (eq 32).

Sequestration/Reagent Capture Using Polymeric-Supported Sulfonic Acid. Bergbreiter[17] has reported the use of Amberlyst 15 as an efficient acid catalyst for the deprotection of Boc-protected amines such as **60** This reaction was performed using an excess of Amberlyst 15 (250% w/w) to convert the deprotected amine to the corresponding ammonium salt (**61**), which was thereby ionically bound to the polymeric supported sulfonate



(32)

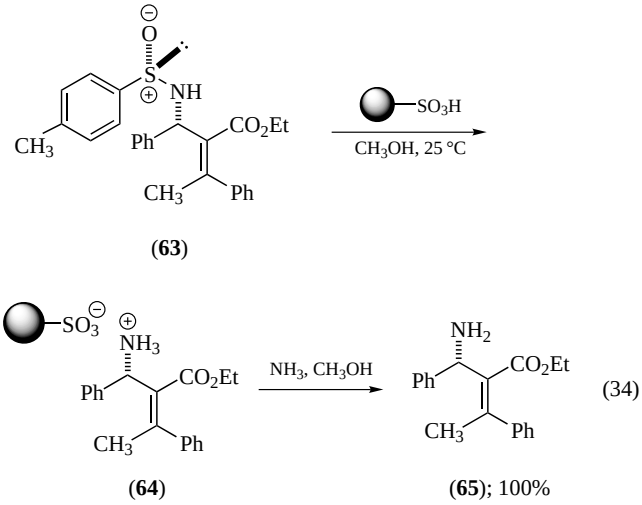
counterion. The captured ammonium salt (**61**) was purified by washing with dichloromethane to remove any of the starting materials and reagents. The required amine was efficiently removed from this resin by shaking with a solution of ammonia in methanol when (*R*)-α-methylbenzylamine (**62**) was obtained in 93% yield (eq 33).



(33)

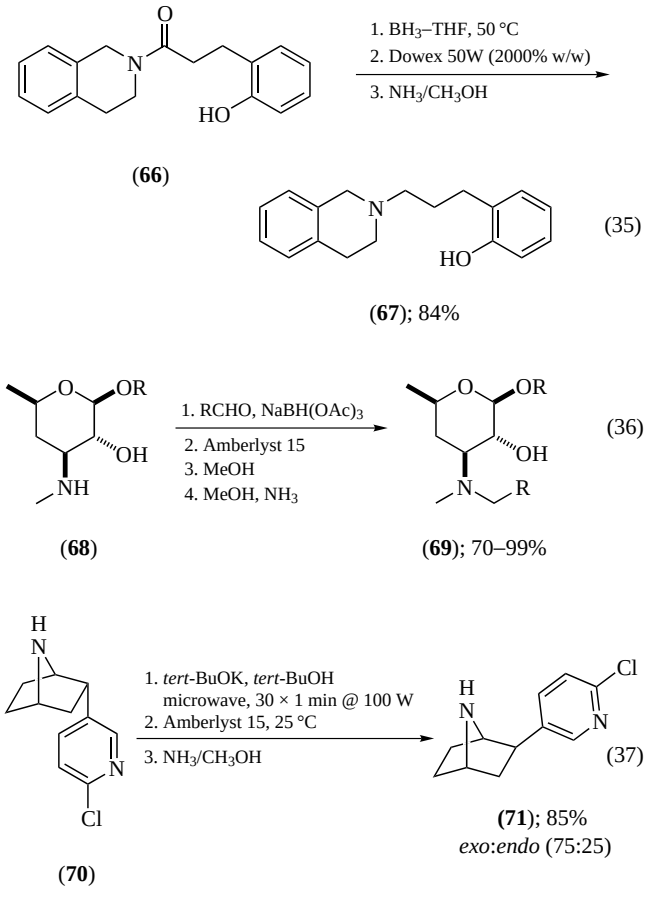
Li[18] has developed a related procedure for the deprotection of an *N*-*p*-toluene sulfinyl group using an excess of Amberlite IR-120 (1000% w/w) in methanol. Addition of *p*-toluenesulfinamide (**63**) to a solution of Amberlite IR-120 in methanol gave the polymeric bound ammonium salt (**64**). The required amine **65** was removed from the resin and isolated in quantitative yield using a solution of ammonia in methanol (eq 34).

The use of a cation scavenging resin, such as the conjugate base of polymeric sulfonic acid, to capture (and purify) organic cations is becoming increasingly common.[4,37] Bussolari[53] has employed this approach to isolate and purify the amine **67** (using Dowex 50W – 2000% w/w) by reductive amination of the amide **66** with borane as the reducing agent (eq 35). This reaction sequence appears to be an efficient method for the synthesis of tertiary amines. Denis[54] has recently reported an extension to



(34)

this reductive amination approach in which a series of secondary amines such as **68** were converted to the corresponding tertiary amines (**69**) by an in situ reductive amination approach involving an aldehyde and $NaBH(OAc)_3$ (eq 36). The required tertiary amines (**69**) were purified and reisolated in good to excellent yield when using Amberlyst 15 as an ammonium capture agent. It was also found that the yields were higher and the purification more reproducible when using Amberlyst 15 rather than Dowex 50W. Ley[55] has also reported the use of Amberlyst 15 as a purification/scavenger reagent in the microwave-mediated synthesis of *rac*-epibatidine (**71**) from its stereoisomer **70** (eq 37).

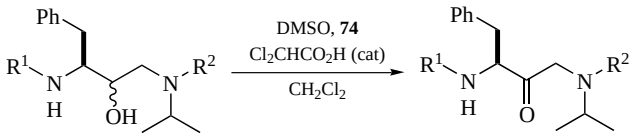


(35)

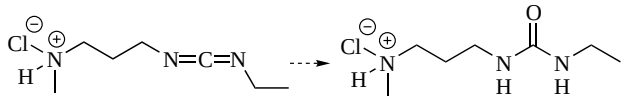
(36)

(37)

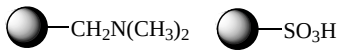
Flynn[56] reported the use of Amberlyst 15 as a reagent to aid purification of a series of ketones shown in **73**, derived from oxidation of an hydroxyethyl amine (**72**) by Moffat oxidation (eq 38). Addition of DMSO, diimide **74**, and a substoichiometric amount of dichloroacetic acid to a solution of **72** in dichloromethane gave **73** in good yield. However, this approach required the removal of the diimide **74** and the associated by-product urea (**75**). An acid scavenger resin (**76**) was initially added to remove HCl from both **74** and **75**, followed by the addition of Amberlyst 15 (**77**) to capture and sequester **74** and **75** in the form of their corresponding ammonium salts **78** and **79** Simple filtration gave the required ketone **73** in moderate yield and purity.



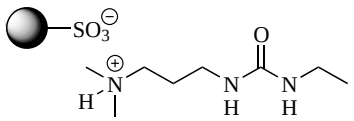
(**72**) (**73**)
48–92% (purity 71–93%)



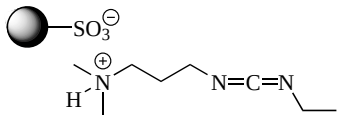
(**74**) (**75**)



(**76**) (**77**)



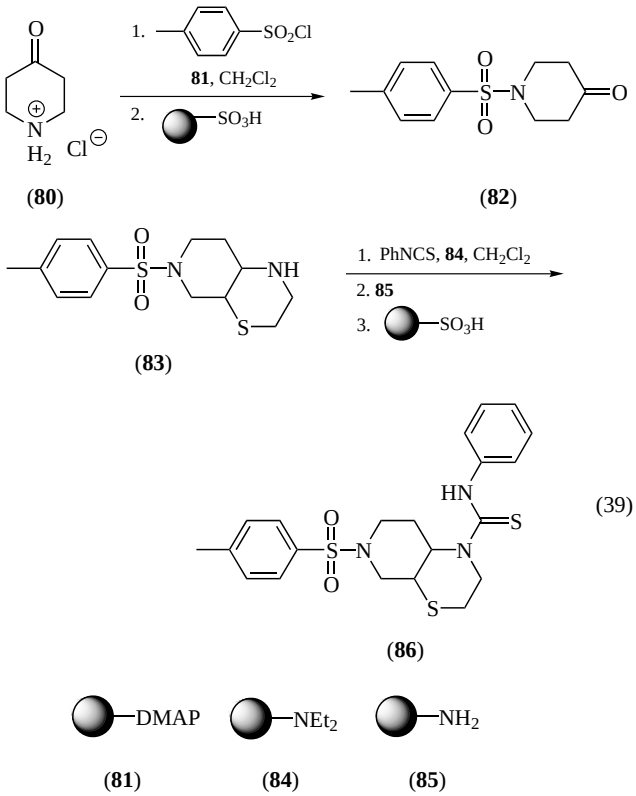
(**78**)



(38)

(**79**)

Ley[34] has reported the use of Amberlyst 15 at several stages of his six-step synthesis of a piperidino-thiomorpholine library, which relied solely on the use of polymeric supported reagents (eq 39). The first step required the formation of a variety of sulfonamides (**82**). These were synthesized by adding an excess of 4-piperidone hydrochloride hydrate (**80**) to a range of commercially available sulfonyl chlorides such as *p*-toluene sulfonyl chloride. The reaction was carried out using predried polymeric supported DMAP (**81**) to give the sulfonamide **82** The remaining amine (derived from **80**) was removed from the solution as sequestered ammonium ion by the addition of Amberlyst 15. In the final stages of the synthetic sequence to the target piperidino-thiomorpholines, Amberlyst 15 assisted in the purification of a series of thioureas such as **86**. For example, following the addition of phenyl isothiocyanate to a solution of amine **83** in dichloromethane in the presence of a polymeric acid scavenger, diethylaminomethyl polystyrene (**84**), the excess quantities of the isothiocyanate were scavenged by the addition of aminomethyl polystyrene (**85**). Treatment of the reaction solution with Amberlyst 15 then gave the required thiourea derivative **86** in excellent purity (eq 39).



(**80**) (**82**)

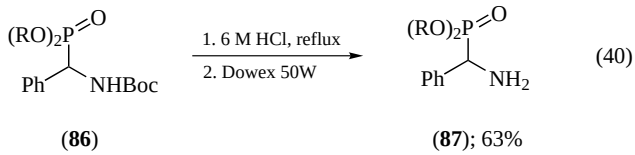
(**83**)

(39)

(**86**)

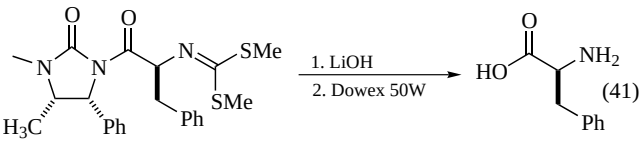
(**81**) (**84**) (**85**)

Purification: Ion-exchange Using Polymeric Supported Sulfonic Acid. Dowex 50W has also found use as an ion-exchange resin for the purification of amine derivatives.[4,37] Hammerschmidt[57] has purified a substituted amine **88**, after a Boc deprotection of **87** with HCl (6 M) (eq 40), whereas Najera used the same resin to purify phenylalanine (**90**) after cleavage from the corresponding oxazolidinone (**89**) with lithium hydroxide (eq 41).[58]



(40)

(**86**) (**87**); 63%



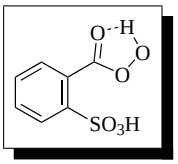
(41)

(**88**); 90% de (**89**); 90% ee; 90%

Related Reagents. *p*-Toluenesulfonic Acid; Amberlyst 15 (20–60 mesh beads); Amberlite IR-120 (8% cross-linked beads); Dowex 50 (2% cross-linked mesh (dry) 50–100 mesh beads); Nafion-H NR50 (10–35 mesh beads; 97% purity).

1. Greenlee, W. J.; Thorsett, E. D., *J. Org Chem.* **1981**, *46*, 5351.
2. Kabza, K. G.; Chapados, B. R.; Gestwicki, J. E.; McGrath, J. L., *J. Org Chem.* **2000**, *65*, 1210.
3. *The Sigma-Aldrich Library of Chemical Safety Data*, 2nd Edn; Lenga, R. E., Ed.; Sigma Aldrich: Milwaukee, 1988, Vol. 1, p 128.
4. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J., *J. Chem Soc., Perkin Trans. 1* **2000**, 3815.
5. Gupta, S. K., *J. Org. Chem.* **1976**, *41*, 2642.
6. Dann, A. E.; Davis, J. B.; Nagler, M. J., *J. Chem Soc., Perkin Trans. 1* **1979**, 158.
7. Yu, L. B.; Chen, D. P.; Li, J.; Wang, P. G., *J. Org. Chem.* **1997**, *62*, 208.
8. Habermann, J.; Ley, S. V.; Scicinski, J. J.; Scott, J. S.; Smits, R.; Thomas, A. W., *J. Chem Soc., Perkin Trans. 1* **1999**, 2425.
9. Patwardham, S. A.; Dev, S., *Synthesis* **1974**, 348.
10. Alexakis, A.; Gardette, M.; Colin, S., *Tetrahedron Lett.* **1988**, *29*, 2951.
11. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S., *Synthesis* **1979**, 618.
12. Nishiguchi, T.; Fujisaki, S.; Kuroda, M.; Kajisaki, K.; Saitoh, M., *J. Org Chem.* **1998**, *63*, 8183.
13. Coppola, G. M., *Synthesis* **1984**, 1021.
14. Beier, R.; Mundy, B. P., *Synth. Comm.* **1979**, *9*, 271.
15. Ballini, R.; Petrini, M., *J. Chem Soc., Perkin Trans. 1* **1988**, 2563.
16. Ballini, R.; Petrini, M., *Synthesis* **1990**, 336.
17. Liu, Y. S.; Zhao, C. X.; Bergbreiter, D. E.; Romo, D., *J. Org Chem.* **1998**, *63*, 3471.
18. Li, G. G.; Kim, S. H.; Wei, H. X., *Tetrahedron* **2000**, *56*, 719.
19. Caycho, J. R.; Tellado, F. G.; deArmas, P.; Tellado, J. J. M., *Tetrahedron Lett.* **1997**, *38*, 277.
20. Baruah, B.; Dutta, M. P.; Boruah, A.; Prajapati, D.; Sandhu, J. S., *Synlett* **1999**, 409.
21. Xu, Z. P.; Chuang, K. T., *Canad. J. Chem. Eng.* **1996**, *74*, 493.
22. Petrini, M.; Ballini, R.; Marcantoni, E.; Rosini, G., *Synth. Commun.* **1988**, *18*, 847.
23. Patwardhan, A. A.; Sharma, M. M., *React. Polym.* **1990**, *13*, 161.
24. Scott, L. T.; Naples, J. O., *Synthesis* **1973**, 209.
25. Habermann, J.; Ley, S. V.; Smits, R., *J. Chem Soc., Perkin Trans. 1* **1999**, 2421.
26. Hansen, M. C.; Verdaguer, X.; Buchwald, S. L., *J. Org Chem.* **1998**, *63*, 2360.
27. Majetich, G.; Khetani, V., *Tetrahedron Lett.* **1990**, *31*, 2243.
28. Schinzer, D.; Ringe, K., *Synlett* **1994**, 463.
29. Righi, G.; D'Achille, R., *Tetrahedron Lett.* **1996**, *37*, 6893.
30. Kosmrlj, J.; Kocevar, M.; Polanc, S., *Synth. Commun.* **1996**, *26*, 3583.
31. Fischer, J.; Holderich, W. F., *Appl. Catal.* **1999**, *180*, 435.
32. Porwanski, S.; Salanski, P.; Descotes, G.; Bouchu, A.; Queneau, Y., *Synthesis* **2000**, 525.
33. Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S., *J. Am. Chem. Soc.* **1997**, *119*, 4874.
34. Habermann, J.; Ley, S. V.; Scott, J. S., *J. Chem. Soc., Perkin Trans. 1* **1998**, 3127.
35. Bussolari, J. C.; Rehborn, D. C.; Combs, D. W., *Tetrahedron Lett.* **1999**, *40*, 1241.
36. Shuker, A. J.; Siegel, M. G.; Matthews, D. P.; Weigel, L. O., *Tetrahedron Lett.* **1997**, *38*, 6149.
37. Eames, J.; Watkinson, M., *Eur. J. Org. Chem.* **2001**, 1213.
38. Yadav, G. D.; Krishnan, M. S., *Org. Process. Res. Dev.* **1998**, *2*, 86.
39. Davies, C. W.; Thomas, G. G., *J. Chem. Soc.* **1952**, 1607.
40. John, E. V. O.; Israelstam, S. S., *J. Org. Chem.* **1961**, *26*, 240.
41. Yamato, T.; Hideshima, C.; Suehiro, K.; Tashiro, M.; Prakash, G. K. S.; Olah, G. A., *J. Org. Chem.* **1991**, *56*, 3955.
42. Yamato, T.; Hideshima, C.; Suehiro, K.; Tashiro, M.; Prakash, G. K. S.; Olah, G. A., *J. Org. Chem.* **1991**, *56*, 6248.
43. Loev, B.; Massengale, J. T., *J. Org. Chem.* **1957**, *22*, 988.
44. Suzuki, E.; Tohmori, K.; Ono, Y., *Chem. Lett.* **1987**, 2273.
45. Scott, L. T.; Naples, J. O., *Synthesis* **1973**, 209.
46. Tius, M. A.; Fauq, A. H., *J. Am. Chem. Soc.* **1986**, *108*, 1035.
47. Birk, C.; Voss, J., *Tetrahedron* **1996**, *52*, 12745.
48. Newman, M. S., *J. Am. Chem. Soc.* **1953**, *75*, 4740.
49. Billimoria, J. D.; Maclagan, N. F., *J. Chem. Soc.* **1954**, 3257.
50. Ballini, R.; Petrini, M., *J. Chem. Soc., Perkin Trans 1* **1988**, 2563.
51. Lorette, N. B., *J. Org. Chem.* **1957**, *22*, 346.
52. Schmidt, B. F.; Snyder, E. J.; Carroll, R. M.; Farnsworth, D. W.; Michejda, C. J.; Smith, R. H., *J. Org. Chem.* **1997**, *62*, 8660.
53. Bussolari, J. C.; Rehborn, D. C.; Combs, D. W., *Tetrahedron Lett.* **1999**, *40*, 1241.
54. Denis, A.; Renou, C., *Tetrahedron Lett.* **2002**, *43*, 4171.
55. Habermann, J.; Ley, S. V.; Scott, J. S., *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253.
56. Flynn, D. L.; Crich, J. Z.; Devraji, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodward, S., *J. Am. Chem. Soc.* **1997**, *119*, 4874.
57. Hammerschmidt, F.; Hanbauer, M., *J. Org. Chem.* **2000**, *65*, 6121.
58. Guillena, G.; Najera, C., *J. Org. Chem.* **2000**, *65*, 7310.

o-Sulfoperbenzoic Acid



[31652-18-3] $C_7H_6O_6S$ (MW 218.20)

InChI = 1/C7H6O6S/c8-7(13-9)5-3-1-2-4-6(5)14(10,11)12/h1-4, 9H,(H,10,11,12)/f/h10H

InChIKey = BMKGRTUNBVSFIY-KZFATGLACA

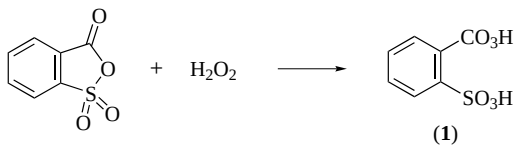
(electrophilic reagent which delivers oxygen to alkenes[1])

Solubility: sol water and aqueous acetone.

Form Supplied in: not available commercially.

Analysis of Reagent Purity: iodometry.[2]

Preparative Methods: *o*-sulfobenzoic anhydride and hydrogen peroxide (30%; 1.3 equiv) react in acetone at −4 to 0 °C to furnish *o*-sulfoperbenzoic acid (**1**) in 65–75% yield (eq 1).

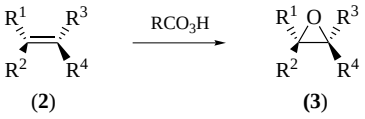


(1)

(**1**)

Handling, Storage, and Precautions: an aqueous acetone solution of the reagent is quite stable at rt and loss of active oxygen amounts to 1–2% per week. Since the reagent is a peroxide and potentially explosive, care is required in carrying out reactions with it. During workup, check for peroxides before solvent removal.

***Anti* Hydroxylation of Alkenes.** Reaction of a peroxycarboxylic acid (RCO_3H) with an alkene (**2**) is *syn* stereospecific;[3] the product is the epoxide (**3**) (eq 2). Under favorable conditions (pH of the reaction medium, temperature) the initially formed epoxide (**3**) undergoes *trans* ring opening due to reaction with RCO_2H and furnishes the diol monoester (**4**) or (**5**) (or a mixture of **4** and **5**); saponification of the diol monoester gives the diol (**6**). Peroxyformic acid (H_2O_2/formic acid) and trifluoroperacetic acid (TFPAA) are the peroxy acids which are normally used to effect the *anti* hydroxylation of alkenes (**2** → **6**). *Anti* addition of hydroxyl groups to alkenes can also be effected by Prevost reaction, which involves treating an alkene with one equivalent of iodine and two equivalents of the silver salt of a carboxylic acid; the monoester of the diol which is obtained is saponified.[4]

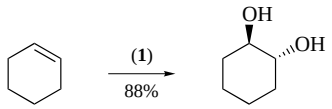


(2)

(**2**) (**3**)

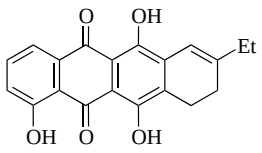
(**4**) R^5 = R(C=O)– (**5**) R^5 = R(C=O)–
(**6**) R^5 = H (**7**) R^5 = H

When an alkene is reacted with the peroxy acid (**1**) in aqueous acetone, the *anti* hydroxylation product is obtained directly. Cyclohexene (**8**) is converted to the *trans*-diol (**9**) (eq 3). Reagent (**1**) has been used for the synthesis of (±) γ-rhodomycinone (**11**) via *trans* hydroxylation of the alkene (**10**) (eq 4).[5]

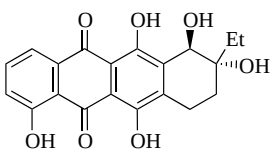


(3)

(**8**) (**9**)



(**10**)



(4)

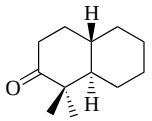
(**11**)

It is of interest to note that the electron-deficient alkene maleic acid has been hydroxylated to furnish tartaric acid in 80% yield. Phenylglyceric acid has been similarly prepared from cinnamic acid.

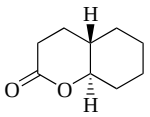
When one of the groups (R^1,R^2,R^3,R^4) attached to the epoxide ring in (**3**) is capable of stabilizing a positive charge on the neighboring carbon, the epoxide can undergo *cis* ring opening.[6]

Epoxidation of Alkenes. Epoxides have been isolated by reacting alkenes with the peroxy acid (**1**) in the presence of a solid buffer such as sodium carbonate. Epoxides have been prepared from α-terpineol and cholesterol in 82% and 89% yields, respectively.

Baeyer–Villiger Reaction. Baeyer–Villiger reaction of cyclohexanone takes place readily at 0 °C with (**1**) (4–6 h) to furnish hexanolide in 80% yield. Peracid (**1**) did not react with the ketone (**12**) and 4,4-dimethylcholestan-3-one. Reaction of (**12**) with peracetic acid–boron trifluoride etherate furnished the lactone (**13**) in 36% yield.[7]



(**12**)



(**13**)

1. Bachhawat, J. M.; Mathur, N. K., *Tetrahedron Lett.* **1971**, 691.
2. Swern, D. In *Organic Peroxides*; Swern, D., Ed.; Wiley: New York, 1970; 1, Chapter 7.
3. Berti, G., *Top. Stereochem.* **1973**, *7*, 93.
4. (a) Haines, A. H., *Comprehensive Organic Synthesis* **1991**, *7*, 437. (b) Sonnet, P. E., *Tetrahedron* **1980**, *36*, 557.
5. (a) Kende, A. S.; Tsay, Y.-G., *Chem. Commun.* **1977**, 140. (b) Braun, M., *Tetrahedron Lett.* **1980**, *21*, 3871.
6. (a) Berti, G.; Bottari, F.; Ferrarini, P. L.; Macchia, B., *J. Org. Chem.* **1965**, *30*, 4091. (b) Rosen, W. E.; Dorfman, L.; Linfield, M. P., *J. Org. Chem.* **1964**, *29*, 1723.
7. Hase, T. A.; Huikko, R., *Acta Chem. Scand.* **1978**, *B32*, 467.

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Sulfur Trioxide[1]

[7446-11-9] O_3S (MW 80.07)
InChI = 1/O3S/c1-4(2)3
InChIKey = AKEJUJNQAAGONA-UHFFFAOYAX

(highly reactive electrophilic agent for replacing (i) a hydrogen atom or other substituent bonded to carbon by an SO_3H or derived sulfo group, forming a carbon–sulfur bond (called sulfonation), (ii) a hydrogen atom bonded to oxygen by an SO_3H group,

forming an oxygen–sulfur bond (called sulfation or *O*-sulfonation, and (iii) a hydrogen atom bonded to nitrogen by an SO_3H group, forming a nitrogen–sulfur bond (called sulfamation or *N*-sulfonation);[1a,1b] reagent for cycloaddition to carbon–carbon double bonds;[1a,2] moderate oxidizing agent[3])

Physical Data: mp 16.8 °C; bp 44.7 °C; *d* 1.970 g cm^{-3}.

Solubility: miscible in all proportions with liquid SO_2; sol dichloromethane, chloroform, carbon tetrachloride, 1,1,1-trichloroethane (some react slowly with SO_3, e.g. CCl_4 yields phosgene);[4] SO_3 in dilute solution (≤10 mol %) in SO_2, CCl_3F, and CCl_4 is present as monomer; at higher concentrations the cyclic trimer is also present;[5] sol nitromethane (reacts at 0–15 °C slowly, and at 25–40 °C sometimes violently to give nitromethanesulfonic acid and other compounds);[6] modestly sol 1,4-dioxane; the resulting complex is unstable;[7,8] the solid adduct can decompose violently on standing for some time at rt;[9] reacts violently with water.

Form Supplied in: liquid/solid, containing 1% of stabilizer to prevent polymerization, in sealed glass container.

Handling, Storage, and Precautions: in the absence of a suitable stabilizer, SO_3 shows a strong tendency to polymerize when exposed even to traces of moisture. Use in a fume hood. Keep the container of SO_3 tightly closed and dry. Upon handling open to air, the liquid gives off fumes of a sulfur trioxide–sulfuric acid spray! Reacts violently with water. Causes burns to the skin; is very toxic by inhalation and if swallowed. Contact with combustible material may cause fire. Wear eye and face protection and suitable protective clothing. In case of contact with eyes, rinse immediately with plenty of water, immediately remove all contaminated clothing and seek medical advice.

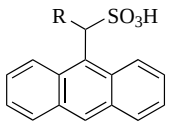
Organic Sulfur Trioxide Reagents. Apart from SO_3 and its less reactive addition compounds, formed with suitable Lewis bases[10] such as pyridine,[11] trimethylamine,[12] dimethyl sulfide,[13] sulfolane,[14] triphenylphosphine,[15,16] triphenylbismuthine,[16] triphenylphosphine oxide,[17] tricylohexyl-[16] and trimethylphosphine oxide,[17] triethyl phosphate,[18] dimethyl sulfoxide,[19] *N*,*N*-dimethylformamide,[20] nitromethane,[21] 1,4-dioxane,[1a–d] and 1,4-oxathiane,[22] there is a class of sulfonating sulfate ester reagents, e.g. dimethyl polysulfate ($MeOSO_2(OSO_2)_n$ OMe)[23] and trimethylsilyl chlorosulfate.[24,25] There are also the protic sulfonating reagents, concentrated aqueous and fuming sulfuric acid, and fluorosulfuric acid, chlorosulfonic acid, and acetylsulfuric acid.[1d] The reactivity order of the Lewis base complexes of SO_3 varies strongly. On the basis of direct experimental evidence[26] and of relative $pK_{B\text{-}SO_3}$ [27] and pK_{BH^+} [28] values, the sulfonation reactivity is suggested to increase in the order trimethylamine–SO_3 < sulfur trioxide–pyridine, DMSO–SO_3 < *N*,*N*-dimethylformamide–SO_3, trimethyl phosphate–SO_3 < sulfur trioxide–1,4-dioxane < sulfolane–SO_3, nitromethane–SO_3.

Aromatic Sulfonation. Reaction of an arene (ArH) with SO_3 leads to sulfonation with formation of arenesulfonic acids ($ArSO_3H$). Mechanistically two different stages can be recognized, viz. 'primary' and 'secondary' sulfonation.[1f,29,30] In the primary stage, arenepyrosulfonic acids (ArS_2O_6H) are formed. A pyrosulfonic acid is a mixed anhydride, liable to disproportionate to give arenesulfonic anhydride and $H_2S_2O_7$.[30b,31–34] Working up the reaction mixture with water and heating the resulting aqueous mixture to reflux for 15 min leads to complete hydrolysis of the pyrosulfonic acids and sulfonic anhydrides to the corresponding arenesulfonic acids.[31] Sulfonylation to give diaryl sulfones is another possible complication in reaction of arenes with SO_3, especially when using deactivated arenes at high concentrations.[1f]

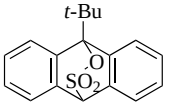
The steric requirements of a sulfonic acid group are very similar to those of a *t*-butyl group and prevent sulfonation *ortho* to a *t*-butyl group. Sulfonation of *t*-butylbenzene with SO_3 gives 98% of the 4-sulfonic acid (4-S), and that of *m*-di-*t*-butylbenzene gives 98% of the 5-S.[35] Reaction of *p*-di-*t*-butylbenzene with SO_3 in CCl_3F yields 58% of *p*-*t*-butylbenzenesulfonic acid by direct sulfo-de-*t*-butylation.[35]

Sulfonic acid isomer distribution data for the SO_3 sulfonation are available for alkylbenzenes[36] and their halogeno derivatives;[37] phenol and anisole,[31,38] and their methyl,[38,39] halogeno,[38,40] and hydroxy and methoxy derivatives;[32,41] and naphthalene,[36] and its methyl,[42] and hydroxy and methoxy derivatives.[34,43] SO_3 sulfonation isomer distribution data are also available for a number of polycyclic aromatic hydrocarbons and 1,6-methano[10]annulenes, including some alkyl derivatives.[36]

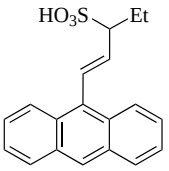
Deviating Sulfonation Behavior of 9-Alkylanthracenes. Reaction of 9-methylanthracene with SO_3 in dioxane leads exclusively to methyl sulfonation to give sulfonic acid (**1**) quantitatively.[44] Under comparable conditions, 9-*t*-butylanthracene gives δ-sultone (**2**).[45a] Sulfonation of 9-pentylanthracene gives predominantly sulfonic acid (**3**) with some (**4**).[45b] The α-alkenyl-γ-sulfonic acid (**3**) is formed via the corresponding 9-alkenylanthracene as an intermediate.[45c]



(**1**) R = H
(**4**) R = Bu



(**2**)



(**3**)

Positional Selectivity. Judging from the data for toluene,[46] *o*-xylene,[47] 1-methylnaphthalene,[42a,48] phenol,[38,49] anisole,[38,49] and 2,3-dihydrobenzofuran[50] and -pyran,[50] the positional selectivity is significantly greater for sulfonation with SO_3 than with sulfuric acid containing 90 wt % H_2SO_4.

For the sulfonation of an (alkyl)arene with SO_3 in differing solvents, the variation in the isomer distribution is limited.[14,51] With phenol and anisole the *ortho*:*para* sulfonation ratio is significantly larger when using CH_2Cl_2 than the complex-forming solvents nitromethane and dioxane.[31] With CH_2Cl_2 the SO_3 forms instead a complex with the C(sp^2) oxygen of the substrate which, as result of intramolecular transfer of SO_3, leads to enhanced *ortho* sulfonation. With substituted phenols and anilines, subject to the positions of the other substituents, the positional selectivity changes very significantly on varying the [SO_3]:[substrate] from ≤1.0 to >4.0 (Table 1).

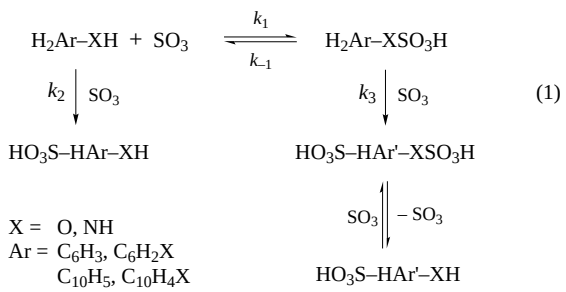
As for the phenol derivatives, this illustrates the importance of the initial sulfation equilibrium (k_1, k_{-1}) (eq 1). Applying ≤1.0

Table 1 Sulfonation of phenol and Aniline derivatives in nitromethane at 0 °C

Substrate[a]	SO_3 (equiv)	Product mixture composition (%)[b]
2-MeO-P[41]	1.0	4-S(76)5-S(24)
	4.0	(19)(81)
	4.0[b]	(<2)(>98)
3,5-Me_2-P[39]	0.9	2-S(89)4-S(11)
	4.0	(25)(75)
2,6-Me_2-P[40b]	0.9	3-S(<2)4-S(>98)
	6.0	(77)(23)
2,6-Me_2-A[40b]	1.0	3-S(<2)4-S(<98)
	8.0	(87)(13)

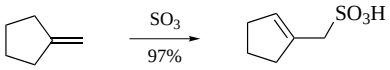
[a] P, A, and S stand for phenol, aniline, and SO_3H, respectively
[b] Reversed addition

equiv SO_3 the effective substrate species being sulfonated is the hydroxyarene H–Ar–OH (k_2), the OH substituent of which is strongly activating and *para* directing, whereas on using a large excess of SO_3 the entity undergoing sulfonation is the corresponding aryl hydrogen sulfate H–Ar–OSO_3H (k_3), the OSO_3H substituent being deactivating and *para* (+ *ortho*) directing. This may accordingly lead to a different substitution pattern. The sulfation equilibrium (k_1, k_{-1}) constant is temperature dependent. Phenol with 1.0 equiv SO_3 in nitromethane at −35 °C is rapidly sulfated to give phenyl hydrogen sulfate quantitatively, which at >0 °C isomerizes to phenol-4-S as the only eventual product.[38] The increase of both the 2- to 3-S ratio in the reaction of *p*-methoxyphenol with 1.5 equiv SO_3,[41] and the 2- to 4-S ratio in the reaction of 1-naphthol with 1.0 equiv SO_3[43a] with increasing reaction temperature, were ascribed to the increase in the k_{-1}/k_1 ratio.

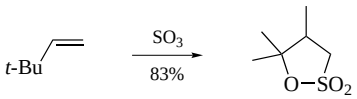


(1)

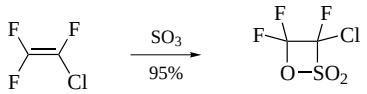
Sulfonation of Unsaturated Aliphatic Compounds. Sulfur trioxide reacts vigorously with linear[52] and branched[53] alkenes to give rise to β-sultones as the primary sulfonation products.[1a,1b,2] Since neat SO_3 is too reactive, complexes of SO_3 with dioxane[8] or pyridine[11] are used to moderate the sulfonation reaction. The formation of β-sultone is stereo- (*syn*) and regioselective, obeying Markovnikov's rule. However, these β-sultones are thermally unstable at rt and their rearrangement leads to complex mixtures of alkenesulfonic acids and γ- and δ-sultones. Yields of the isolated alkenesulfonic acids (eq 2)[54] and sultones (eq 3)[53] vary considerably with the alkene structure and reaction conditions. Halogenated,[1h] in particular fluorinated,[1i] ethylenes react with SO_3 to give relatively stable halogenated β-sultones. This cycloaddition of SO_3 at the double bond proceeds in a regioselective way (eq 4).[55]



(2)

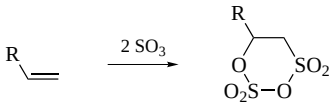


(3)



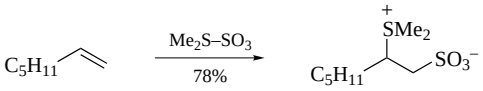
(4)

Reaction of an alkene with an excess of SO_3 gives a cyclic sulfonate–sulfate anhydride, also referred to as carbyl sulfate or pyrosulfate (eq 5).[56] This carbyl sulfate is formed by a slow insertion of SO_3 into the intermediate β-sultone.[52a] The complex of sulfur trioxide with dimethyl sulfide reacts with alkenes and alkynes to afford sulfobetaines in good yields (eq 6).[13,57] These sulfobetaines are produced by nucleophilic attack of the dimethyl sulfide on the initially formed β-sultones.



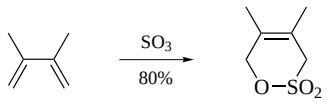
(5)

R = H, 94%; Me, 94%; 2,6-$Cl_2C_6H_3$, 96%



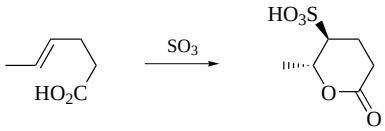
(6)

Conjugated dienes are sulfonated by sulfur trioxide reagents to give β-unsaturated δ-sultones (eq 7). The yields vary strongly; they increase with the number of alkyl substituents at the 2- and 3-positions of the alkadiene.[58]

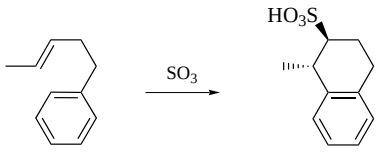


(7)

Functionalized alkenes containing a phenyl or carboxylic acid group at appropriate distance from the double bond undergo intramolecular cyclization during the sulfonation.[59] On reaction of (*E*)-4-hexenoic acid[59a] with SO_3 a sulfo-δ-lactone is formed (eq 8), and a Friedel–Crafts type cyclization is observed on sulfonation of (*E*)-5-phenyl-2-pentene[59b] (eq 9); both cyclizations proceed quantitatively and stereospecifically.

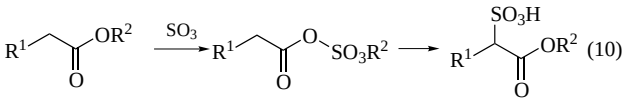


(8)



(9)

Sulfonation of Saturated Aliphatic Compounds. Sulfur trioxide reacts with aliphatic acids[60] or esters[61] to give, initially, insertion of SO_3 into the carboxylic acid or ester group, followed by sulfonation at the α-carbon (eq 10). Reactions of aldehydes and ketones with SO_3 also afford the α-sulfonated products.[62]



(10)

R^1 = H, alkyl; R^2 = H, alkyl

It should be noted that sulfonation of linear alkylbenzenes, linear long-chain α-alkenes, and fatty esters and the sulfation of fatty alcohols by SO_3–air mixtures are widely applied processes in industry for the production of surfactants.[63]

Related Reagents. Dimethyl Sulfoxide–Sulfur Trioxide/Pyridine; Sulfur Trioxide–1,4-Dioxane; Sulfur Trioxide–Pyridine.

1. (a) Gilbert, E. E., *Chem. Rev.* **1962**, *62*, 549. (b) Gilbert, E. E. *Sulfonation and Related Reactions*; Interscience: New York, 1965; Chapters I and II. (c) Gilbert, E. E., *Synthesis* **1969**, 3. (d) Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Interscience: New York, 1968; Chapters 1 and 2. (e) Cerfontain, H., *J. Org. Chem.* **1982**, *47*, 4680. (f) Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 153. (g) *The Chemistry of Sulphonic Acids, Esters and Derivatives*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1991; Chapters 10, 19, 22. (h) Knunjanz, I. L.; Sokolski, G. A., *Angew. Chem.* **1972**, *11*, 623. (i) Mohtasham, J.; Gard, G. L., *Coord. Chem. Rev.* **1992**, *112*, 47.
2. Roberts, D. W.; Williams, D. L., *Tetrahedron* **1987**, *43*, 1027.
3. Mark, V.; Zengierski, L.; Pattison, V. A.; Walker L. E., *J. Am. Chem. Soc.* **1971**, *93*, 3538.
4. Oddo, G.; Sconzo, A., *Gazz. Chim. Ital.* **1927**, *57*, 83 (*Chem. Abstr.* **1927**, *21*, 1771).
5. Gillespie, R. J.; Robinson, E. A., *Can. J. Chem.* **1961**, *39*, 2189.
6. Terent'ev, A. P.; Yanovskaya, L. A.; Berlin, A. M.; Borisov, E. A., *Vestn. Mosk. Univ. Fiz.-Math. Estestven. Nauk* **1953**, 117 (*Chem. Abstr.* **1955**, *49*, 8092f).
7. Bordwell, F. G.; Crosby, G. W., *J. Am. Chem. Soc.* **1956**, *78*, 5367.
8. Suter, C. M.; Evans, P. B.; Kiefer, J. M., *J. Am. Chem. Soc.* **1938**, *60*, 538.
9. Sisler, H. H.; Audrieth, L. F., *Inorg. Synth.* **1946**, *2*, 173.
10. Baumgarten, P., *Chem. Ber.* **1926**, *59*, 1166.
11. (a) Scully, J. F.; Brown, E. V., *J. Org. Chem.* **1954**, *19*, 894. (b) Terent'ev, A. P.; Dombrovskii, A. V., *J. Gen. Chem. USSR (Engl. Transl.)* **1949**, *19*, 1467.
12. Burg, A. B., *J. Am. Chem. Soc.* **1943**, *65*, 1629.
13. Nagayama, M.; Okumura, O.; Yaguchi, K.; Mori, A., *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2473.
14. Hayashi, T.; Iida, H.; Ogata, I., *J. Appl. Chem. Biotechnol.* **1976**, *26*, 513 (*Chem. Abstr.* **1977**, *86*, 50 108n).
15. Galpin, I. J.; Kenner, G. W.; Marston, A.; Mills, O. S., *J. Chem. Soc., Chem. Commun.* **1981**, 789.
16. Becke Goehring, M.; Thielemann, H., *Z. Anorg. Allgem. Chem.* **1961**, *308*, 33 (*Chem. Abstr.* **1961**, *55*, 21 937h).
17. Burg, A. B.; McKee, W. E., *J. Am. Chem. Soc.* **1951**, *73*, 4590.
18. Sakota, N.; Kohora, K., *Nippon Kagaku Zasshi* **1965**, *86*, 747 (*Chem. Abstr.* **1966**, *65*, 667h).
19. Whistler, R. L.; King, A. H.; Ruffini, G.; Lucas, F. A., *Arch. Biochem. Biophys.* **1967**, *121*, 358 (*Chem. Abstr.* **1967**, *67*, 79 018b).
20. (a) Kenner, G. W.; Stedman, R. J., *J. Chem. Soc* **1952**, 2069. (b) Wolfram, M. L.; Han, T. M. S., *J. Am. Chem. Soc.* **1959**, *81*, 1764.
21. Cerfontain, H.; Koeberg-Telder, A., *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 569.
22. Quaedvlieg, M., *Methoden Org. Chem. (Houben-Weyl)* **1955**, *9*, 364.
23. Van Wazer, J. R.; Grant, D.; Dungan, C. H., *J. Am. Chem. Soc.* **1965**, *87*, 3333.
24. (a) Birot, M.; Dunogues, J.; Duffaut, N.; Calas, R.; Lefort, M., *Bull. Soc. Clem. Fr.* **1978**, *1*, 442. (b) Bourgeois, P.; Duffaut, N., *Bull. Soc. Chem. Fr.* **1980**, *2*, 195.
25. (a) Hofmann, K.; Simchen, G., *Liebigs Ann. Chem.* **1982**, *282*. (b) Hofmann, K.; Simchen, G., *Liebigs Ann. Chem.* **1984**, 39.
26. De Wit, P.; Kruk, C.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 266.
27. Auger, Y.; Delesalle, G.; Fischer, J. C.; Wartel, M., *J. Electroanal. Chem.* **1980**, *106*, 149 (*Chem. Abstr.* **1980**, *92*, 153 823v).
28. (a) Lowry, T. H.; Schueller-Richardson, K. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 297. (b) Ege, S. N. *Organic Chemistry*, 2nd ed.; Heath: Lexington, MA, 1989.
29. (a) Christensen, N. H., *Acta Chem. Scand.* **1963**, *17*, 2253. (b) Christensen, N. H., *Acta Chem. Scand.* **1964**, *18*, 954. (c) Guyer, P.; Fleury, R.; Reich, H. U., *Chimia* **1968**, *22*, 40.
30. (a) Bosscher, J. K.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 873. (b) *Tetrahedron* **1968**, *24*, 6543.
31. Ansink, H. R. W.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 183.
32. Cerfontain, H.; Ansink, H. R. W.; Coenjaarts, N. J.; De Graaf, E. J.; Koeberg-Telder, A., *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 445.
33. Ansink, H. R. W.; De Graaf, E. J.; Zelvelder, E.; Cerfontain, H., *Can. J. Chem.* **1993**, *71*, 210.
34. Ansink, H. R. W.; Zelvelder, E.; De Graaf, E. J.; Cerfontain, H., *J. Chem. Soc., Perkin Trans. 2* **1993**, 721.
35. Ris, C.; Cerfontain, H., *J. Chem. Soc., Perkin Trans. 2* **1975**, 1438.
36. Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 153 (Tables III–V).
37. Cerfontain, H.; Koeberg-Telder, A.; Laali, K.; Lambrechts, H. J. A.; De Wit, P., *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 390.
38. Cerfontain, H.; Koeberg-Telder, A.; Lambrechts, H. J. A.; De Wit, P., *J. Org. Chem.* **1984**, *49*, 4917.
39. Goossens, H. D.; Lambrechts, H. J. A.; Cerfontain, H.; De Wit, P., *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 426.
40. (a) De Wit, P.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 121, 418. (b) De Wit, P.; Woldhuis, A. F.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 668.
41. Cerfontain, H.; Coenjaarts, N. J.; Koeberg-Telder, A., *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 7.
42. (a) Lammertsma, K.; Cerfontain, H., *J. Chem. Soc., Perkin Trans. 2* **1979**, 673. (b) Lambrechts, H. J. A.; Cerfontain, H., *Tetrahedron* **1982**, *38*, 1667.
43. (a) Ansink, H. R. W.; Zelvelder, E.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 210. (b) Ansink, H. R. W.; Zelvelder, E.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 216. (c) Ansink, H. R. W., De Graaf, E. J.; Zelvelder, E.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 499.
44. Cerfontain, H.; Koeberg-Telder, A.; Ris, C.; Schenk, C., *J. Chem. Soc., Perkin Trans. 2* **1975**, 966.
45. (a) Van de Griendt, F.; Cerfontain, H., *Tetrahedron Lett.* **1978**, 3263. (b) Van de Griendt, F.; Cerfontain, H., *J. Chem. Soc., Perkin Trans. 2* **1980**, 13. (c) Van de Griendt, F.; Cerfontain, H., *J. Chem. Soc., Perkin Trans. 2* **1980**, 19.

46. (a) Van Albada, M. P.; Cerfontain, H.; Koeberg-Telder, A., *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 33. (b) Cerfontain, H.; Sixma, F. L. J.; Vollbracht, L., *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 659.
47. (a) Cerfontain, H.; Koeberg-Telder, A.; Van Kuipers, E., *J. Chem. Soc., Perkin Trans. 2* **1972**, 2091. (b) Prinsen, A. J.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 833.
48. Lammertsma, K.; Verlaan, C. J.; Cerfontain, H., *J. Chem. Soc., Perkin Trans. 2* **1978**, 719.
49. Cerfontain, H.; Lambrechts, H. J. A.; Schaasberg Nienhuis, Z. R. H.; Coombes, R. G.; Hadjigeorgiou, P.; Tucker, G. P., *J. Chem. Soc., Perkin Trans. 2* **1985**, 659.
50. Ansink, H. R. W.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 395.
51. El Homsi, A.; Gilot, B.; Canselier, J-P., *J. Appl. Chem. Biotechnol.* **1978**, *28*, 405 (*Chem. Abstr.* **1979**, *90*, 121 114g).
52. (a) Bordwell, F. G.; Peterson, M. L., *J. Am. Chem. Soc.* **1954**, *76*, 3952. (b) Püschel, F.; Kaiser, C., *Chem. Ber.* **1965**, *98*, 735.
53. (a) Bordwell, F. G.; Chapman, R. D.; Osborne, C. E.; *J. Am. Chem. Soc.* **1959**, *81*, 2002. (b) Robbins, M. D.; Broaddus, C. D., *J. Org. Chem.* **1974**, *39*, 2459.
54. Arnold, R. T.; Amidon, R. W.; Dodson, R. M., *J. Am. Chem. Soc.* **1950**, *72*, 2871.
55. Dmitriev, M. A.; Sokol'skii, G. A.; Knunyants, I. L., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1960**, 792.
56. (a) Breslow, D. S.; Hough, R. R., *J. Am. Chem. Soc.* **1957**, *79*, 5000. (b) Weinreich, G. H.; Jufresa, M., *Bull. Soc. Chem. Fr.* **1965**, 787. (c) Sheehan, J. C.; Zoller, U., *J. Org. Chem.* **1975**, *40*, 1179.
57. Shastin, A. V.; Popkova, T. V.; Balenkova, E. S.; Bel'skii, V. K.; Lazhko, E. I., *J. Org. Chem. USSR (Engl. Transl.)* **1987**, *23*, 2039.
58. (a) Schonk, R. M.; Bakker, B. H.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 201. (b) Akiyama, T.; Sugihara, M.; Imagawa, T.; Kawanisi, M., *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1251.
59. (a) Schonk, R. M.; Bakker, B. H.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 389. (b) *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 478.
60. Truce, W. E.; Olson, C. E., *J. Am. Chem. Soc.* **1953**, *75*, 1651.
61. Smith, F. D.; Stirton, A. J., *J. Am. Oil Chem. Soc.* **1967**, *44*, 405 (*Chem. Abstr.* **1967**, *67*, 90 351a).
62. Truce, W. E.; Alfieri, C. C., *J. Am. Chem. Soc.* **1950**, *72*, 2740.
63. Surfactant Science Series *Anionic Surfactants*; Linfield, W. M., Ed.; Dekker: New York, 1976; Vol. 7.

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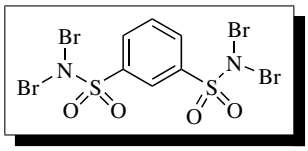
N, N, N′, N′-Tetrabromobenzene-1,3-disulfonamide (TBBDS)



[848408-54-8] $C_6H_4Br_4N_2O_4S_2$ (MW 551.85)

InChI = 1/C6H4Br4N2O4S2/c7-11(8)17(13,14)5-2-1-3-6(4-5)18(15,16)12(9)10/h1-4H

InChIKey = QIUSYTGYTFWFKM-UHFFFAOYAH

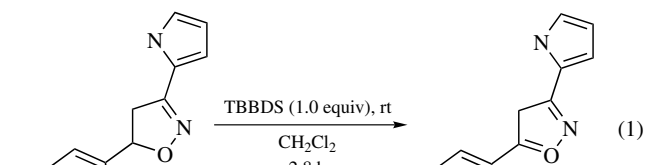
(reagent used as a source of Br^+ for oxidation reactions)

Physical Data: mp 267–270 °C.[1]

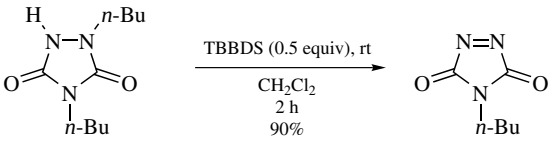
Preparative Methods: prepared from benzene-1,3-disulfonylamide.[2]

Handling, Storage, and Precautions: TBBDS is stable for 3–4 months under atmospheric conditions.

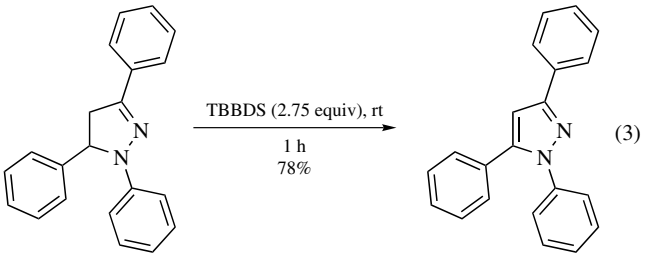
Oxidative Aromatization of Heterocycles. TBBDS permits the oxidation of many five-membered heterocycles providing good to excellent yields of the corresponding aromatized compounds. Isoxazolines are oxidized to isoxazoles relatively rapidly within a few hours at room temperature (eq 1).[2] The most effective conversions occur when the molar ratio of isoxazolines to TBBDS is 1:1, thus providing the desired products in good yields ranging from 65 to 98%. Urazoles are also oxidized to their corresponding triazolinediones under mild and heterogeneous conditions with excellent yields (eq 2),[3] thus avoiding difficult isolation and purification of the sensitive triazolinediones. In the presence of TBBDS, pyrazolines are converted to pyrazoles (eq 3).[4,5] No side products are observed whether the reactions are conducted in solution,[5] in solvent-free conditions,[4,5] at room temperature, or under microwave conditions.[4] TBBDS overcomes most of the drawbacks of the classical oxidizing agents used for the aromatization of heterocycles such as Pd/C/AcOH[6] or activated carbon/O_2.[7] Indeed, the methods based on the traditional oxidizing reagents suffer from long reaction times, high temperatures, formation of side products, difficulty in removing the reagents, and high toxicity of the reagents, whereas the use of the inexpensive TBBDS allows relatively rapid reactions under mild conditions. In addition, the sulfonamide can be easily recovered at the end of the reaction and reused many times without any notable reduction of its efficiency.



(1)

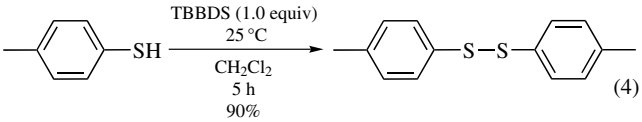


(2)



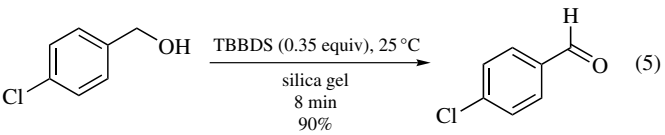
(3)

Oxidation Reactions. Aromatic and aliphatic thiols react efficiently with TBBDS at room temperature to give the corresponding disulfides in good to excellent yields (eq 4).[8] The yield of these oxidations is not affected by the electronic and/or steric variation of the thiols, and other oxidizable functional groups are kept unchanged during the reaction. TBBDS is a stable, inexpensive, easily handled, and environmentally sound oxidizing agent compared to the agents usually employed for the conversion of thiols to disulfides.[9]



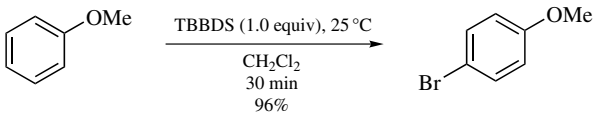
(4)

In another fashion, alcohols are easily oxidized to the corresponding aldehydes or ketones under solvent-free conditions in good to excellent yields.[10] One major asset of this method is that no overoxidation to carboxylic acids is observed (eq 5). It is noteworthy that other oxidants such as TEMPO[11] or bismuth derivatives[12] usually require heat, longer reaction times, or the addition of several other reagents that are toxic.



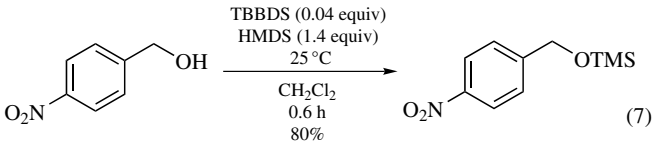
(5)

Bromination Reactions. TBBDS is able to brominate aromatic rings containing ortho- and para-directing groups in a highly selective process (eq 6).[1] Unlike other standard halogenation conditions,[13] this new method does not require the addition of any Lewis acid and tolerates various functional groups on the aromatic ring such as aldehydes.[14] Other advantages of this new bromination method are high yields, simplicity of the reaction conditions, short reaction times, lack of side products, and nontoxicity of the reagent. In addition to that, the recovered starting material can be rebrominated to regenerate the TBBDS without any detectable loss of reactivity.

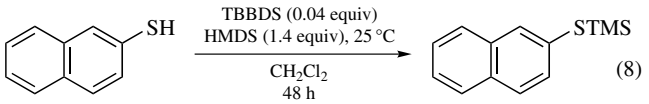


(6)

Silylation Reactions. In the presence of TBBDS, the weak silylating capability of hexamethyldisilazanes (HMDS) toward alcohols and thiols is enhanced.[15] The desired silylated compounds are then isolated in very good yields without side product formation (eqs 7 and 8). The reaction is highly chemoselective because no halogenation of the aromatic ring [1] is observed. The use of microwave or solvent-free conditions fails to convert the alcohols and thiols to the corresponding oxidized compounds.[15] TBBDS is a heterogeneous, recyclable, and noncorrosive catalyst in contrast to the classical catalysts used to activate HMDS such as sulfuric acid[16] or nitrogen–ligand complexes of metal chlorides.[17]

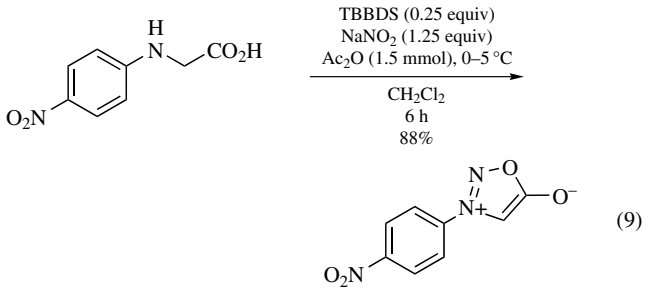


(7)



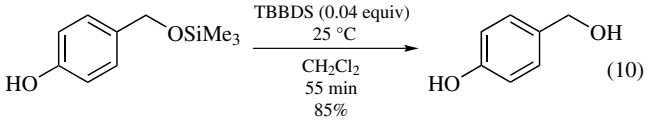
(8)

Nitrosation Reaction. In the presence of TBBDS, *N*-arylglycines are converted to sydnones in a one-pot fashion through *N*-nitrosation followed by cyclization.[18] This reagent permits the realization of this process under neutral conditions, thus avoiding the usual presence of strong acid such as nitrous acid.[19] Using sodium nitrite and acetic anhydride at 0 °C, the desired sydnones are obtained in excellent yields (85–95%) within 5–8 h (eq 9). According to the experimental results, the most effective conversion occurs when the molar ratio of *N*-arylglycines to TBBDS is 4.



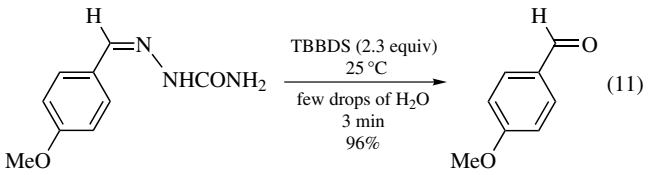
(9)

Deprotection of Silylated Ethers. TBBDS is also an efficient catalyst for the deprotection of alcoholic and phenolic silyl ethers.[10] In the presence of an aprotic solvent such as dichloromethane and some drops of H_2O, the alcohols are isolated in good to excellent yields (eq 10). The reaction is highly chemoselective bacause no halogenation of the aromatic ring[1] occurs, and no overoxidation of the newly liberated alcohol to the corresponding aldehyde is observed. For this reaction again, the sulfonamide can be recovered and reused with no decrease in its catalytic activity.



(10)

Deprotection of Semicarbazones. Semicarbazones are deprotected to regenerate the carbonyl compounds using TBBDS under mild and solvent-free conditions.[20] No side product is formed during the reaction, thus allowing the regeneration of the carbonyl compounds in good to excellent yields (eq 11). This solvent-free method is superior to conventional deprotection methods that require reflux conditions, long reaction times, and use toxic metal ions as catalysts.[21–23] In addition, TBBDS can be regenerated at the end of the reaction by simple bromination of the recovered material, and it can be reused without any notable reduction of its efficiency.



(11)

1. Ghorbani-Vaghei, R.; Jalili, H., *Synthesis* **2005**, 1099.
2. Azarifar, D.; Maleki, B.; Mohammadi, K., *Heterocycles* **2007**, *71*, 683.
3. Zolfigol, M. A.; Ghorbani-Vaghei, R.; Mallakpour, S.; Chehardoli, G.; Choghamarani, A. G.; Yazdi, A. H., *Synthesis* **2006**, 1631.
4. Ghorbani-Vaghei, R.; Azarifar, D.; Maleki, B., *J. Chin. Chem. Soc.* **2004**, *51*, 1373.
5. Ghorbani-Vaghei, R.; Azarifar, D.; Khazaei, A.; Maleki, B., *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 1877.
6. Nakamichi, N.; Kawashita, Y.; Hayashi, M., *Org. Lett.* **2002**, *4*, 3955.
7. Nakamichi, N.; Kawashita, Y.; Hayashi, M., *Synthesis* **2004**, 1015.
8. Ghorbani-Vaghei, R.; Zolfigol, M. A.; Moshfeghifar, N.; Koukabi, N.; Chehardoli, G., *J. Chin. Chem. Soc.* **2007**, *54*, 791.
9. Iranpoor, N.; Firouzabadi, H.; Zolfigol, M. A., *Synth. Commun.* **1998**, *28*, 367.
10. Ghorbani-Vaghei, R.; Amiri, M.; Chegny, M.; Veisi, H., *S. Afr. J. Chem.* **2007**, *60*, 58.
11. Zhao, X.-F.; Zhang, C., *Synthesis* **2007**, 551.
12. Matano, Y.; Suzuki, T.; Shinokura, T.; Imahori, H., *Tetrahedron Lett.* **2007**, *48*, 2885.
13. Olah, G. A.; Kuhn, S. J.; Hardie, B. A., *J. Am. Chem. Soc.* **1964**, *86*, 1055.
14. Khan, S. A.; Munawar, M. A.; Siddiq, M., *J. Org. Chem.* **1988**, *53*, 1799.
15. Ghorbani-Vaghei, R.; Zolfigol, M. A.; Chegeny, M.; Veisi, H., *Tetrahedron Lett.* **2006**, *47*, 4505.
16. Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P., *Chem. Rev.* **2004**, *104*, 199.
17. Firouzabadi, H.; Sardarian, A. R.; Khayat, Z.; Karimi, B.; Tangestaninejad, S., *Synth. Commun.* **1997**, *27*, 2709.
18. Azarifar, D.; Ghasemnejad-Bosra, H.; Ghorbani-Vaghei, R.; Tajbaksh, M., *Heterocycles* **2006**, *68*, 2343.
19. Thoman, C. J.; Voaden, D. J., *Org. Synth., Coll. Vol.* **1973**, *5*, 962.

20. Ghorbani-Vaghei, R.; Shahbazee, E., *J. Braz. Chem. Soc.* **2005**, *16*, 647.
21. Ballini, R.; Bosica, G.; Maggi, R.; Sartori, G., *Synlett* **1997**, 795.
22. Curini, M.; Rosati, O.; Pisani, E.; Costantino, U., *Synlett* **1996**, 333.
23. Kumar, P.; Hegade, V. R.; Pandey, B.; Ravindranathan, R., *J. Chem. Soc., Chem. Commun.* **1993**, 1553.

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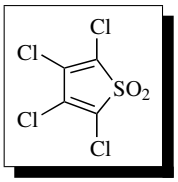
Tetrachlorothiophene Dioxide

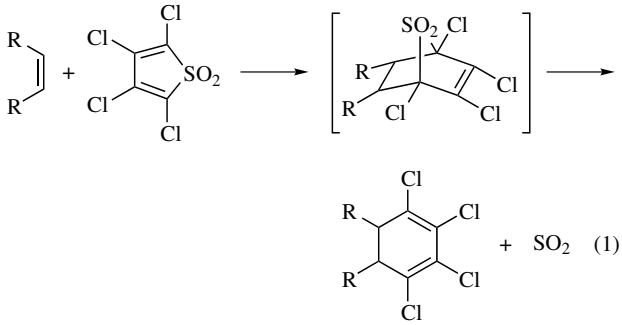


[72448-17-0] $C_4Cl_4O_2S$ (MW 253.92)
InChI = 1/C4Cl4O2S/c5-1-2(6)4(8)11(9,10)3(1)7
InChIKey = IEEFYTGFZKXEEU-UHFFFAOYAO

(reagent used for the annelation of tetrachlorocyclohexa-1,3-diene and, in a broader sense, of benzene to olefinic double bonds)

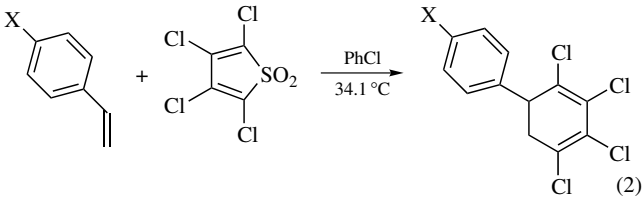
Physical Data: white solid, mp 90–92 °C.[1]
Solubility: soluble in organic solvents.
Preparative Methods: the title reagent can be prepared by oxidation of tetrachlorothiophene with 3-chloroperbenzoic acid [1] or with trifluoroperacetic acid.[2]
Purity: recrystallization from hexane and sublimation at 60 °C and 0.1 Torr.
Handling, Storage, and Precaution: can be stored in a refrigerator for weeks but should be sublimed before use.

Cycloaddition with Alkenes. Tetrachlorothiophene dioxide (TCTD) undergoes a [4 + 2]cycloaddition with olefins to give an unstable 7-thiabicyclo[2.2.1]heptene dioxide which rapidly extrudes SO_2 in a cheletropic reaction yielding a 1,2,3,4-tetrachlorocyclohexa-1,3-diene (eq 1). The primary product has never been observed but it seems plausible as with 3,4-dichlorothiophene dioxide the analogous 7-thiabicyclo[2.2.1]heptene dioxide can be obtained.[3] The broad scope of this reaction is given in the pioneering paper of Raasch.[1]



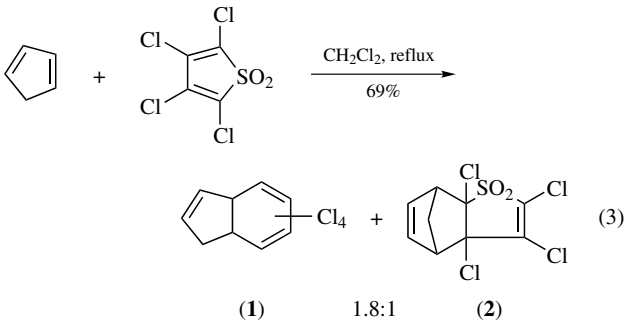
(1)

The cycloaddition of TCTD clearly shows an inverse electron demand but under harsher conditions it does add to maleic anhydride and to *p*-benzoquinone. In a study with *p*-substituted styrenes (eq 2) the addition of TCTD follows the Hammett equation $\log(k/k_H) = -0.84\,\sigma_p^+$ indicating a rate increase with electron donating substituents X.[4]



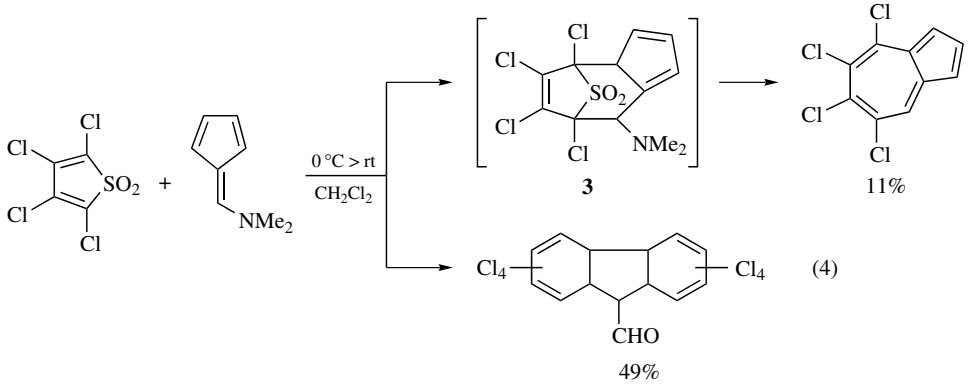
(2)

With 1,3 conjugated dienes TCTD reacts as a diene as well as a dienophile. With cyclopentadiene this dichotomy is shown by the formation of the dihydroindene (**1**) and the tricyclic sulfone (**2**) in a 1.8:1 ratio (eq 3).[1]



(**1**) 1.8:1 (**2**) (3)

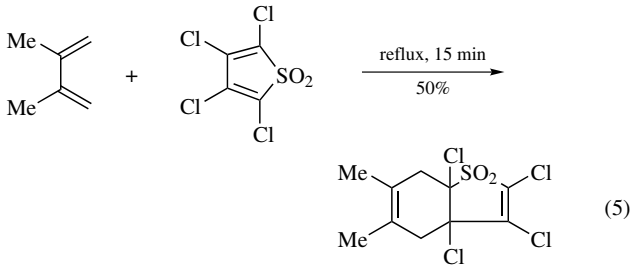
6-Dimethylaminofulvene also reacts with TCTD in two ways (eq 4): The main product results from the [4 + 2]cycloaddition



3 11% 49% (4)

to both endocyclic double bonds, the minor product tetrachloroazulene, however, arises from a [6 + 4]cycloaddition via the not isolated sulfone (**3**).[4]

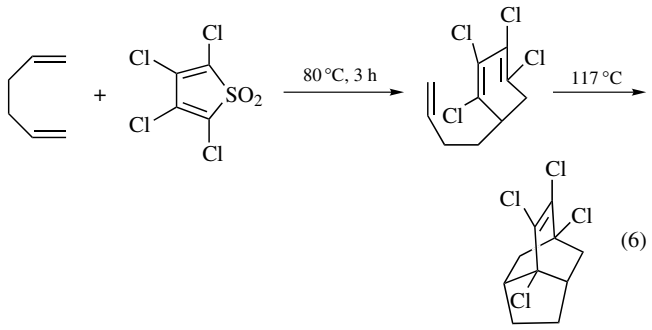
To dimethylbutadiene TCTD adds only as a dienophile to give the bicyclic sulfone (**4**) (eq 5).[1]



(5)

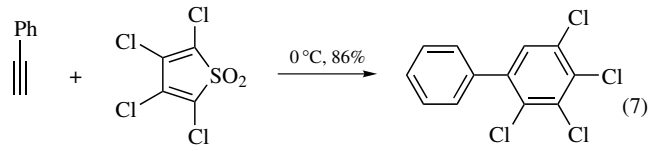
(**4**)

1,5- and 1,6-Dienes in their reaction with TCTD use the fact that the tetrachlorocyclohexadiene formed by the first addition is an enophile. For entropic reason the second double bond prefers the intramolecular [4 + 2]addition to form a cage compound (eq 6).[1]



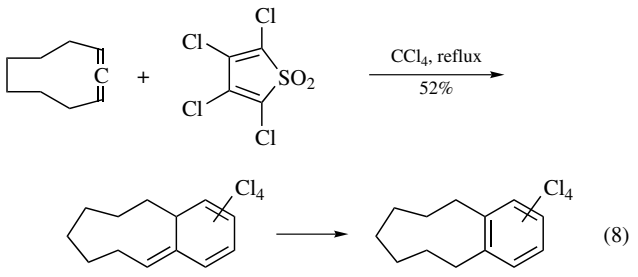
(6)

Phenylacetylene reacts with TCTD exothermally (eq 7) but other alkynes appear to be unreactive.[1]



(7)

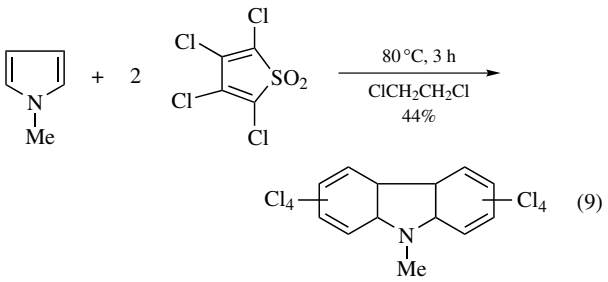
The allene cyclonona-1,2-diene adds to TCTD yielding the tetrachloro-isotoluene (**5**) which under acidic conditions isomerizes to tetrachlorobenzocyclononene (eq 8).[5]



(8)

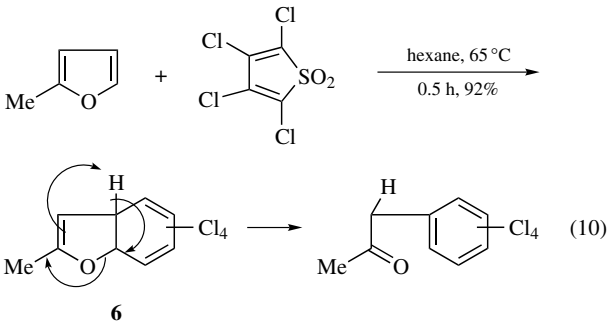
5

There is no example of the addition of TCTD to a benzenoid double bond but the electron rich aromatic five ring heterocycles *N*-methylpyrrole (eq 9) and thiophene undergo a twofold addition.[1]



(9)

The mono adduct of substituted furans, e.g., of 2-methylfuran (**6**) aromatizes under the reaction conditions to a tetrachlorobenzylcarbonyl compound via a retro-oxo-ene reaction (eq 10). The high bond energy of the carbonyl group drives this process, that does not occur with the analogous mono adduct of pyrroles and thiophenes.[3]

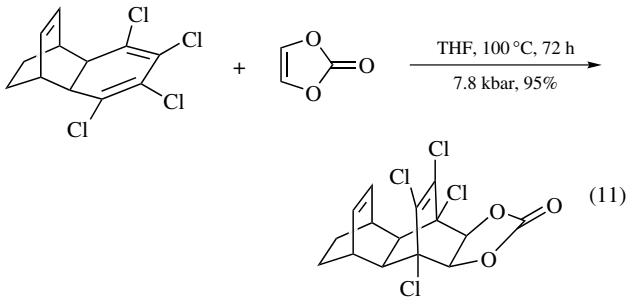


(10)

6

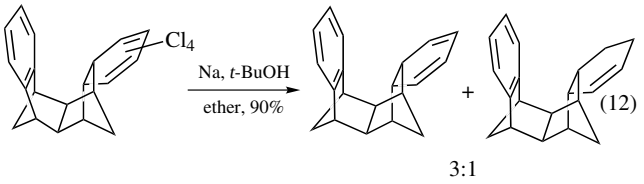
Subsequent Reactions of 1,2,3,4-Tetrachlorocyclohexadienes.

[4 + 2]Cycloaddition. As mentioned above, tetrachlorocyclohexadienes from the mono addition of TCTD to 1,5- and 1,6-dienes undergo an intramolecular addition with the remaining double bond. The intermolecular version of this addition has been used successfully in the construction of many polycyclic compounds. For example, the tetrachlorodiene from TCTD and dihydrobarrelene adds ethene, strained olefins, or electron rich equivalents of ethyne, e.g., vinylene carbonate, to form sesquibicyclo[2.2.2] octenes in good yield (eq 11).[6]

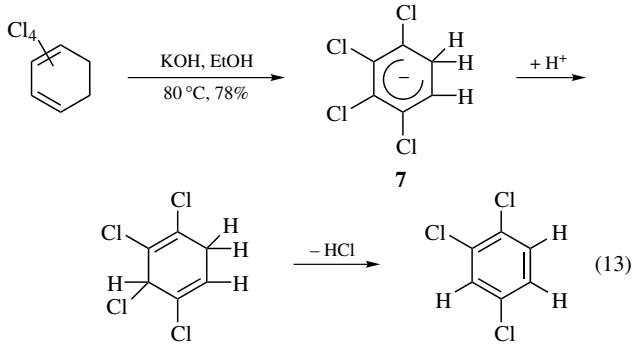


(11)

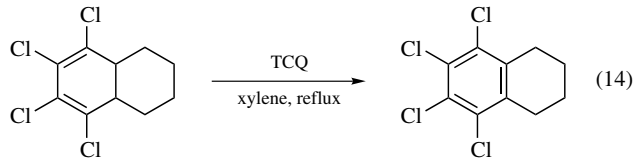
Dechlorination. The reductive dechlorination of tetrachlorocyclohexadienes with sodium in ethanol or in liquid ammonia is difficult to stop at the diene stage, usually one double bond of the diene system is also reduced. However, the deschloro-diene can be obtained under controlled conditions at low temperatures (eq 12).[6,7]



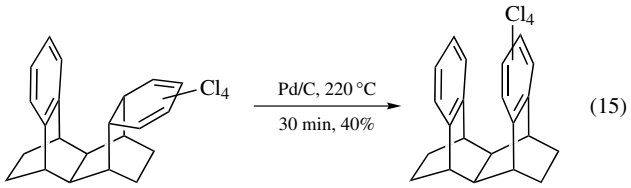
Dehydrochlorination. From tetrachlorocyclohexadienes HCl is eliminated by boiling with potassium hydroxide in ethanol. Exclusively 1,2,4-trichlorobenzenes are formed as the reaction passes a tetrachlorocyclohexa-1,4-diene stage.[8] The abstraction of a proton from tetrachlorocyclohexa-1,3-diene leads to the cyclohexadienyl anion (**7**) that is reprotonated in the 3 position - as in the Birch reduction - to tetrachlorocyclohexa-1,4-diene. From here the 1,4-elimination of HCl leads to 1,2,4-trichlorobenzene (eq 13).[1]



Dehydrogenation. Tetrachlorocyclohexadienes are aromatized by quinones with high oxidation potentials as tetrachloro-*p*-benzoquinone (TCQ) or dichlorodicyano-*p*-benzoquinone (DDQ) (eq 14).[1,9]

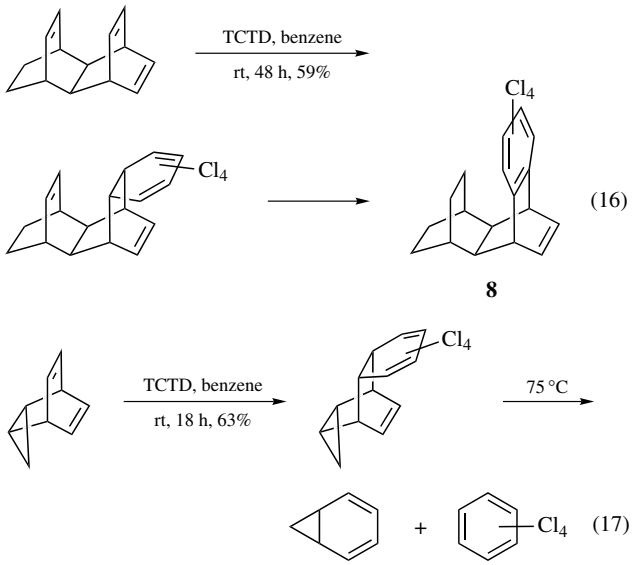


Occasionally, the dehydrogenation by a quinone may fail as the hydrogen atoms to be abstracted are shielded. In this instance an intensive mixing of the substrate with palladium on charcoal and heating has proved successful (eq 15).[6,10]

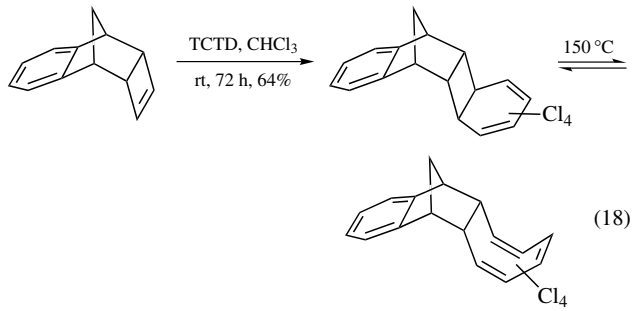


A special case of this dehydrogenation is given by the intramolecular dyotropic hydrogen transfer. In the addition of TCTD to dehydrosesquibicyclo[2.2.2]octene the primary tetrachlorocyclohexadiene undergoes a rapid dyotropic hydrogen shift to give the tetrachlorobenzo-condensed product (**8**) (eq 16).[11]

Extrusion of Tetrachlorobenzene. Tetrachlorocyclohexadienes from the addition of TCTD to one of the etheno bridges of norbornadiene or bicyclo[2.2.2]octadiene undergo cycloreversion to tetrachlorobenzene and a 1,3-diene (eq 17).[12] This reaction is used in the synthesis of some difficult to obtain cyclopentadienes or cyclohexadienes.



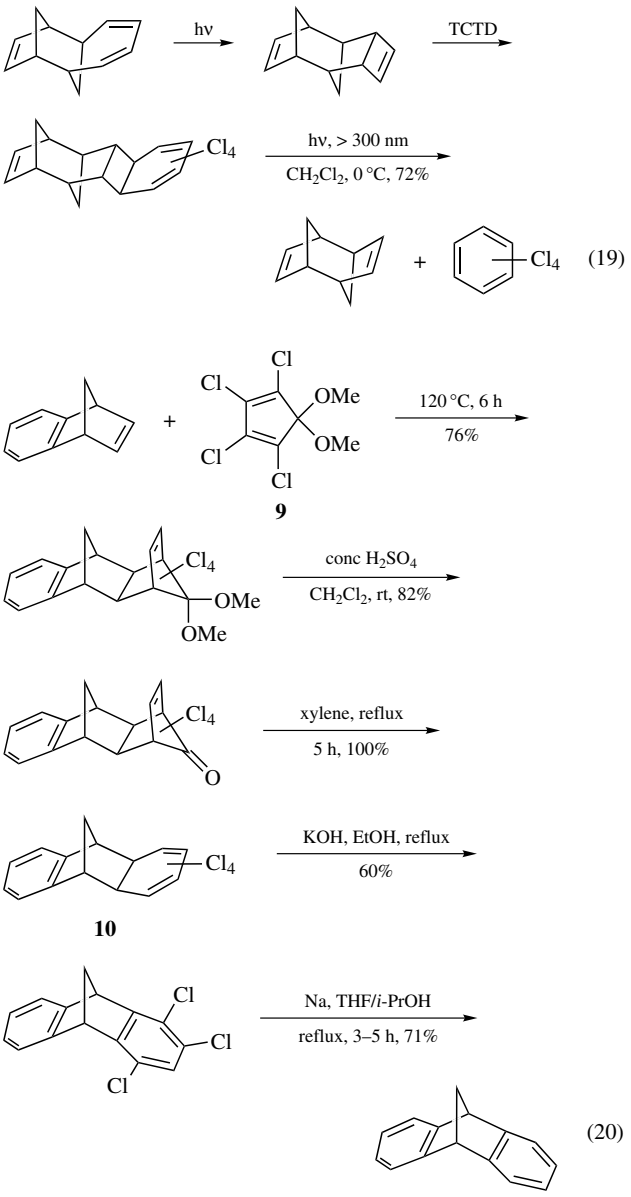
The addition of TCTD to a cyclobutene gives rise to a bicyclo[4.2.0]octadiene which depending on its molecular structure can isomerize to a cyclooctatriene (eq 18).[13]

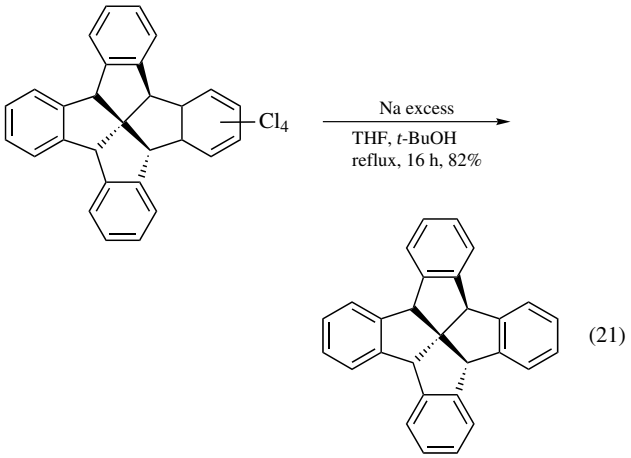


In other cases the tetrachlorobicyclo[4.2.0]octadiene cleaves off tetrachlorobenzene when irradiated through quartz glass with a low pressure mercury lamp.[14] In this reaction the cyclobutene ring of the educt becomes degraded which is of synthetic value if the cyclobutene ring results from a photolytic ring contraction (eq 19)[15] or from a Diels-Alder reaction with 7,8-dichlorobicyclo-[4.2.0]octadiene.

Alternative Reagents for the Annulation of Tetrachlorocyclohexadiene. The cycloaddition of 5,5-dimethoxytetrachlorocyclopentadiene (**9**) to olefins requires higher temperatures than that of TCTD and is also characterized by an inverse electron demand. Hydrolysis of the resulting tetrachloroketal needs strong acid and the tetrachloronorbornenone obtained extrudes CO at temperatures of 80–180 °C. The reaction sequence for the annelation of benzene to benzonorbornadiene using (**9**) is given in eq 20.[16] The last two steps from tetrachlorocyclohexadiene (**10**) to dibenzonorbornadiene represent the standard procedure for the transformation of a tetrachlorocyclohexa-1,3-diene to the benzene ring. In more recent work, however, this process is achieved in one step only as described in the benzoannelation

of tribenzofenestrene (eq 21).[17,18] Dimethoxytetrachlorocyclopentadiene is less expensive than TCTD and commercially available.

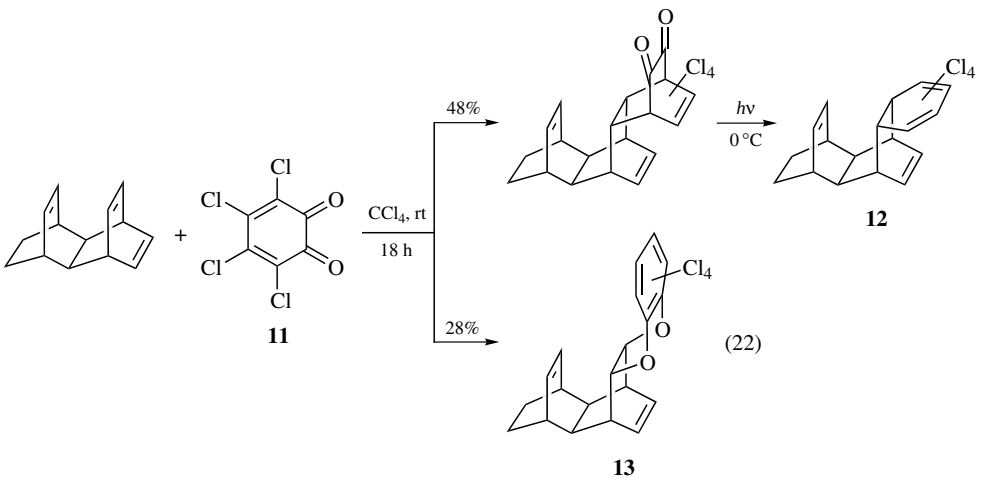


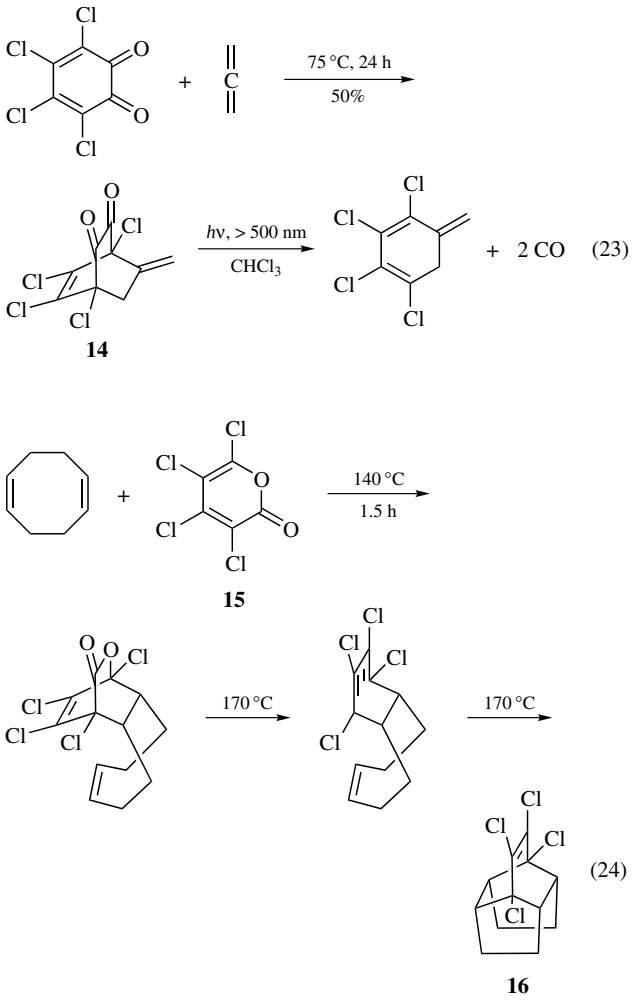


Tetrachloro-*o*-benzoquinone (*o*-chloranil **11**) in cycloadditions to olefins is as reactive as TCTD. The resulting tetrachlorobicyclo[2.2.2]octene-5,6-dione can be bis-decarbonylated by irradiation with a tungsten lamp through pyrex at rt or below. For the synthesis of thermolabile tetrachlorocyclohexadienes as (**12**) this is of advantage (eq 22).[6] A dihydrobenzo-1,4-dioxene (**13**) resulting from the [8 + 2]cycloaddition of the olefin to the carbonyl groups of the *o*-benzoquinone often accompanies the [4 + 2]adduct and in some cases is the only product. Due to its high oxidation potential tetrachloro-*o*-benzoquinone dehydrogenates cyclohexadienes present in the substrate. Tetrachloro-*o*-benzoquinone is commercially available

Tetrachloro-*o*-benzoquinone adds to allene to give the α-diketone (**14**) which after irradiation yields tetrachloro-isotoluene (eq 23).[19]

Tetrachloro-α-pyrone (**15**) has been added to cycloocta-1.5-diene at 140 °C. With loss of CO_2 the same tricyclus (**16**) is formed as in the addition of TCTD (eq 24);[1] with other alkenes, however, the products differ from those obtained with TCTD.





14 (23)

15

(24)

16

1. Raasch, M. S., *J. Org. Chem.* **1980**, *45*, 856.
2. Lou, Y.; Chang, J.; Jorgensen, J.; Lemal, D. M., *J. Am. Chem. Soc.* **2002**, *124*, 15302.
3. Raasch, M. S., *J. Org. Chem.* **1980**, *45*, 867
4. Kanematsu, K.; Kazunobe, H.; Dantsuji, H., *Heterocyles* **1981**, *16*, 1145.
5. Raasch, M. S.; Smart, B. E., *J. Am. Chem. Soc.* **1979**, *101*, 7733.
6. Grimme, W.; Pohl, K.; Wortmann, J.; Frowein, D., *Liebigs Ann. Chem.* **1996**, 1905.
7. Fessner, W. D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H., *J. Am. Chem. Soc.* **1987**, *109*, 4626.
8. Lay, W. P.; Mackenzie, K.; Telford, J. R., *J. Chem. Soc. C* **1971**, 3199.
9. Pritschins, W.; Grimme, W., *Tetrahedron Lett.* **1979**, *47*, 4545.
10. Prinzbach, H.; Sedelmeier, G.; Krüger, C.; Goddard, R.; Martin, H. D.; Gleiter, R., *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 288.
11. Grimme, W.; Wortmann, J.; Frowein, D.; Lex, J.; Chen, G.; Gleiter, R., *J. Chem. Soc., Perkin Trans. 2* **1998**, 1893.
12. Reinhardt, G.; (1982); Dissertation; University of Cologne.
13. Pliskat, H.; (1996); Dissertation; University of Cologne.
14. Nunn, E. E.; Wilson, W. S.; Warrener, R. N., *Tetrahedron Lett.* **1972**, 175.
15. Grimme, W.; Schumachers, L.; Roth, W. R.; Breuckmann, R., *Chem. Ber.* **1981**, *114*, 3197.
16. Paddon-Row, M. N.; Cotsaris, E.; Patney, H. K., *Tetrahedron* **1986**, *42*, 1779.
17. Kuck, D., *Chem. Ber.* **1994**, *127*, 409.
18. Tobe, Y.; Kawaguchi, M.; Kakiuchi, K.; Naemura, K., *J. Am. Chem. Soc.* **1993**, *115*, 1173.
19. Grimme, W.; Härter, M. W.; Sklorz, C. A., *J. Chem. Soc., Perkin Trans. 2* **1999**, 1959.

Wolfram Grimme
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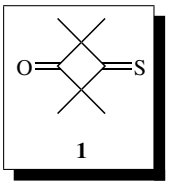
2,2,4,4-Tetramethylcyclobutan-1-one-3-thione



1

[10181-59-6] $C_8H_{12}OS$ (MW 156.25)
InChI = 1/C8H12OS/c1-7(2)5(9)8(3,4)6(7)10/h1-4H3
InChIKey = SVRXPTCPQFXZSF-UHFFFAOYAT

(reagent used as a stable thioketone and a model for the comparison of the reactivities of strained carbonyl and thiocarbonyl groups)

Alternate Name: 2,2,4,4-tetramethyl-3-thioxocyclobutanone, 2,2,4,4-tetramethyl-3-thio-1,3-cyclobutanedione.

Physical Data: mp 57–58 °C.

Solubility: soluble in chlorinated hydrocarbons, hydrocarbons, ethers, alcohols, pyridine, and other commonly used organic solvents; insoluble in water.

Form Supplied in: red crystals, commercially not available.

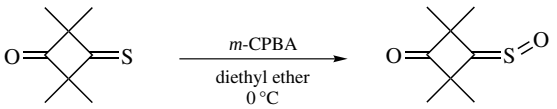
Analysis of Reagent Purity: ^{1}H-NMR, ^{13}C-NMR, single crystal X-ray analysis.[1]

Preparative Methods: the title reagent can be prepared by thionation of 2,2,4,4-tetramethylcyclobutane-1,3-dione with P_4S_{10} in pyridine at 110 °C.[2–4]

Purity: column chromatography (silica gel, hexane/dichloromethane); sublimation.

Handling, Storage, and Precaution: camphoraceous odor; store in a refrigerator, safe in handling.

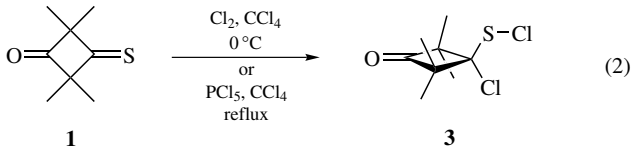
Oxidation Reaction. Treatment of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**1**) with *m*-CPBA in diethyl ether (or dichloromethane) at 0 °C gives the colorless sulfine (thioketone *S*-oxide, **2**) in 80% yield (eq 1).[5] The same product is reported to be formed by sensitized photochemical oxidation of **1** with O_2/methylene blue in chloroform.[6]



1 **2** (1)

The chlorination of **1** with gaseous chlorine in tetrachloromethane at 0 °C[7] or with phosphorus pentachloride in boiling

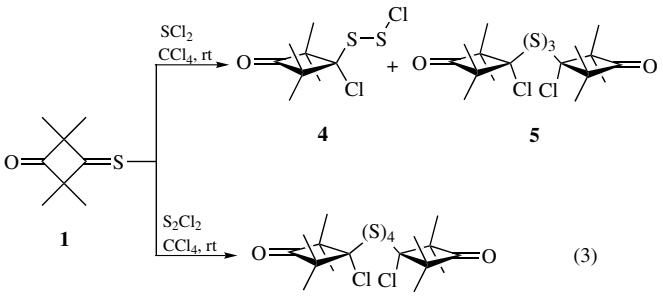
tetrachloromethane[8] affords the stable α-chloro sulfanyl chloride (**3**) (eq 2). Phosphorus pentachloride can be replaced by sulfuryl chloride (SO_2Cl_2).



(2)

1 **3**

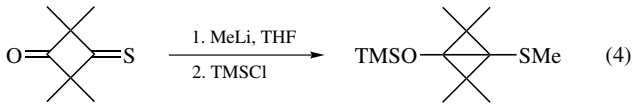
Sulfur dichloride in tetrachloromethane adds easily to **1** to give disulfanyl chloride **4** along with trisulfane **5** as a side product.[8,9] In an analogous reaction, disulfur dichloride and **1** react slowly and tetrasulfane **6** is formed as the exclusive product (eq 3).[8]



(3)

1 **4** **5** **6**

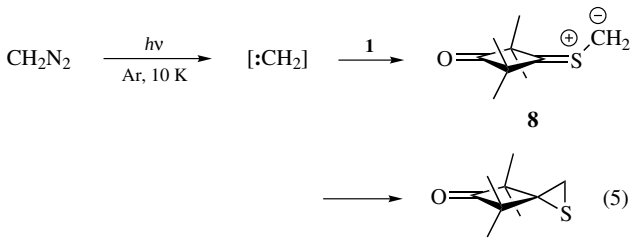
Reactions with Organometallics. Treatment of a mixture of **1** and alkyl bromides in THF with magnesium leads chemoselectively to 3-alkylthio-2,2,4,4-tetramethylcyclobutanones in a thiophilic addition of the in situ generated Grignard reagent.[10] The thiophilic addition is also observed with methyllithium, and quenching with TMSCl results in the formation of bicyclo[1.1.0] butane (**7**) (eq 4).[11]



(4)

1 **7**

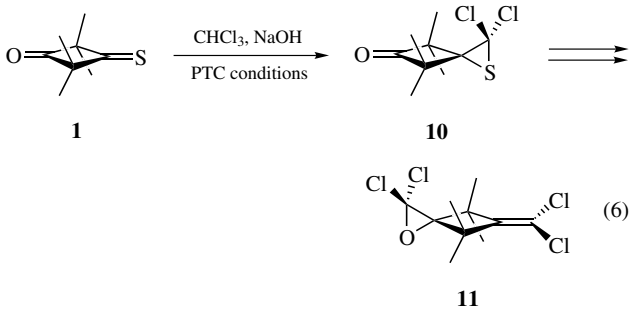
Reactions with Carbenes and Carbenoids. Photochemical decomposition of diazomethane in the presence of **1** in an argon matrix at 10 K yields thiocarbonyl *S*-methylide (**8**) via addition of methylene to the sulfur atom.[12] While increasing the temperature, **8** undergoes a 1,3-dipolar electrocyclization to give thiirane **9** (eq 5).



(5)

8 **9**

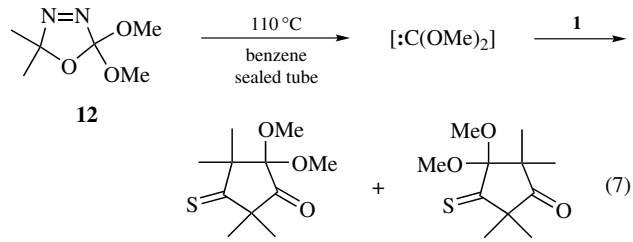
Under PTC conditions, involving chloroform and aqueous sodium hydroxide, **1** is converted into the *gem*-dichlorothiirane (**10**), which subsequently undergoes desulfurization and, finally, the C=O group is transformed into a stable *gem*-dichlorooxirane (**11**) (eq 6).[13]



(6)

1 **10** **11**

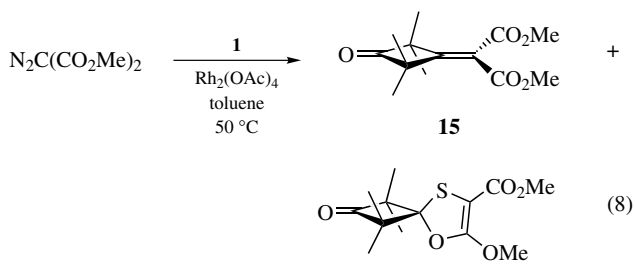
When Seyferth's reagent [(phenyl)(trichloromethyl)mercury] is decomposed in boiling benzene in the presence of **1**, 84% of thiirane **10** is obtained. Through the use of (phenyl)(trifluoromethyl)mercury and sodium iodide under the same conditions, **1** is converted in 50% yield into the difluoro analog of **10**.[14] Unexpectedly, difluorocarbene generated from bis(trifluoromethyl)cadmium in trichloromethane at $-20 \rightarrow 20\,^{\circ}C$ reacts with 2 equiv of **1** to give, in addition to the difluorothiirane derivative, 2,2-difluoro-1,3-dithiolane (a so-called Schönberg product, cf. ref 15) as the product of the interception of the intermediate thiocarbonyl *S*-difluoromethylide by **1**.[16] In contrast to halogenated carbenes, the nucleophilic dimethoxycarbene, generated by thermolysis of **12**, reacts with **1** to give the ring enlarged products **13** and **14** in favor of **13** (eq 7).[17] Remarkably, no dimethoxy thiirane derivative of **1** can be detected.



(7)

12 **13** **14**

The decomposition of dimethyl diazomalonate with $Rh_2(OAc)_4$ in toluene at 50 °C in the presence of **1** leads to two products **15** and **16**, which are formed via an intermediate thiocarbonyl ylide (eq 8). Whereas 1,3-dipolar electrocyclization affords a thiirane which spontaneously extrudes sulfur to give **15**, the competitive 1,5-dipolar electrocyclization yields 1,3-oxathiole **16**.[18]

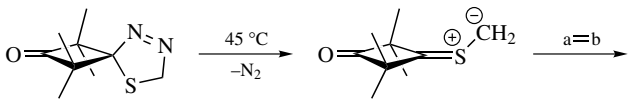


(8)

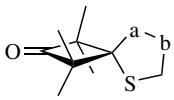
15 **16**

Reactions with 1,3-Dipoles.

Diazo Compounds. Diazomethane reacts immediately with **1** dissolved in diethyl ether in a regioselective manner to give 2,5-dihydro-1,3,4-thiadiazole (**17**) as a relatively stable solid.[19,20] This compound is a superior precursor of the reactive thiocarbonyl *S*-methylide (**8**, eq 9) as it smoothly eliminates nitrogen at 45 °C. In the absence of an appropriate interceptor, thiirane **9** is formed.[21] In the presence of electron-deficient dipolarophiles, diverse five-membered spiro-heterocycles (**18**) are formed via 1,3-dipolar cycloaddition (eq 9).[22,23] Representative examples of dipolarophiles leading to **18** in high yield are DMAD, *N*-phenyl maleinimide, chloral, dimethyl azodicarboxylate, adamantanethione, as well as **1**.[21]



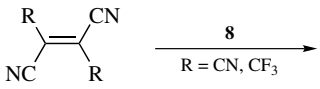
17 **8**



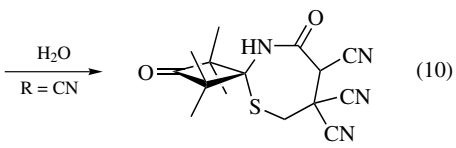
(9)

18

The formation of 1,3-oxathiolane with chloral and 1,3-dithiolanes with cycloaliphatic thioketones occurs regioselectively to yield the sterically less hindered products.[15] On the other hand, aromatic thioketones, e.g., thiobenzophenone or 9*H*-fluorene-9-thione, intercept **8** to give comparable amounts of both regioisomeric adducts. Usually, stereoisomeric dipolarophiles such as fumaronitrile and maleonitrile as well as dimethyl fumarate and maleate form **18** in a stereoselective manner. However, in the case of extremely electron-poor dipolarophiles, e.g., dimethyl 1,2-dicyanofumarate or (*E*)-1,2-bis(trifluoromethyl)ethylene-1,2-dicarbonitrile, non-stereospecific formations of the corresponding tetrahydrothiophenes are described.[24,25] This result is interpreted in terms of a stepwise reaction mechanism with a zwitterion as the key intermediate.[25,26] Alternatively, this intermediate can cyclize to form seven-membered ketenimines of type **20**. With R = CF_3, this product can be isolated in a crystalline form, whereas in the case of R = CN, stable lactam **21** is obtained only after addition of water (eq 10).



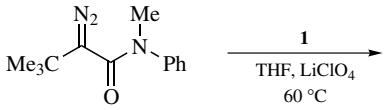
19 **20**



(10)

21

2-Diazopropane reacts with **1** at 0 °C to yield the stable 2,2-dimethyl analog of **17**, which is used as a precursor of the *S*-isopropylide of **1**.[27] The 2,2-diphenyl analog of **17**, prepared from **1** and diphenyldiazomethane, extrudes nitrogen spontaneously leading to the corresponding thiirane.[27] Similarly, EDA and **1** react at rt to give a thiirane-2-carboxylate, which can be desulfurized to yield an ethyl cyclobutylidene acetate.[28] The reactions of **1** with less reactive diazocompounds such as diazoketones, diazoamides, and diazoesters are accelerated by addition of $LiClO_4$, and thiiranes and/or 1,3-oxathioles are obtained.[28–31] Products of both types are formed in the case of α-diazoamide (**22**) (eq 11).



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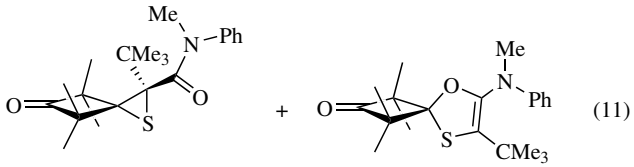
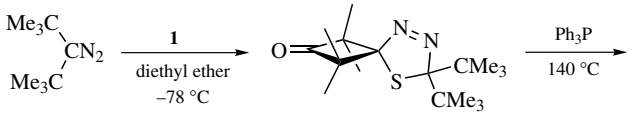


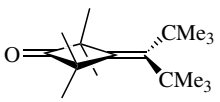
(11)

23 **24**

With a more complex diazo compound containing amino and ester groups, products resulting from 1,3- and 1,5-dipolar electrocyclization are obtained.[32] 'Two-fold extrusion' reactions with **1** and diverse diazo compounds are reported to be aimed at the preparation of sterically crowded ethylenes.[33,34] An example with bis(*tert*-butyl)diazomethane (**25**) is shown in eq 12.



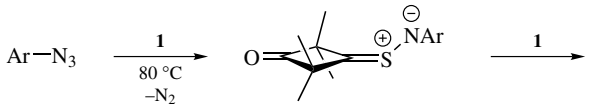
25 **26**



(12)

27

Organic Azides. The 1,3-dipolar cycloadditions of **1** with organic azides require elevated temperatures. Typical products of the reactions of thioketones are *N*-substituted imines, which are formed after decomposition of the initially formed 1,2,3,4-thiatriazole derivates.[35,36] However, in the case of **1** and aryl azides, the intermediate thiocarbonyl *S*-imides (**28**) intercept **1** to give dispiro-1,4,2-dithiazoles (**29**) (eq 13).[37]



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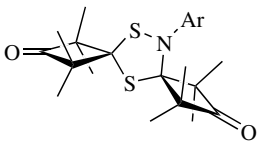
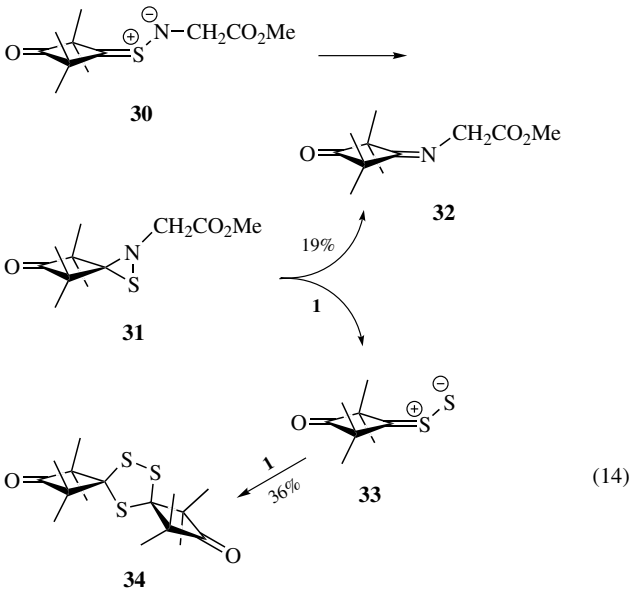


(13)

29

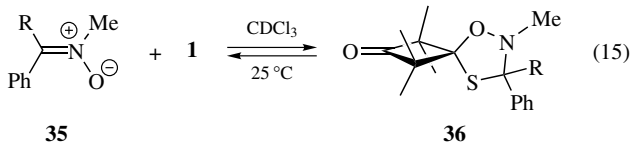
The analogous reaction of **1** with benzyl azide leads to a rearrangement of the corresponding *N*-benzyl derivative of **28** via a 1,4-H shift.[38] In some cases, e.g., methyl azidoacetate, the sulfur atom extruded in the course of the reaction is intercepted by **1** to give a thiocarbonyl *S*-sulfide (thiosulfine, **33**), which subsequently undergoes a 1,3-dipolar cycloaddition with **1** yielding 1,2,4-trithiolane (**34**).[36] Thiaziridine (**31**) formed by ring-closure of **30** is a plausible sulfur donator (eq 14).



(14)

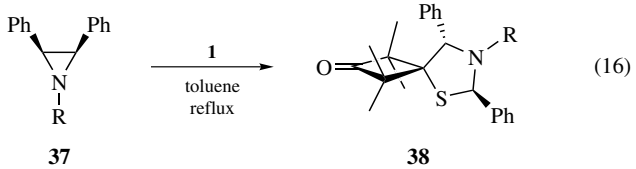
In a three-component reaction with **1** and fumaronitrile dissolved in phenyl azide, the *N*-phenyl substituted thiocarbonyl *S*-imide (**28**, Ar = Ph) cycloadds to fumaronitrile to give the corresponding 1,2-thiazolidine derivative.[32]

Nitrones. 1,3-Dipolar cycloadditions of nitrones with **1** occur regioselectively and 1,4,2-oxathiazolidines of type **36** are obtained in high yield. Aldonitrones are more reactive than ketonitrones.[3] When stored in $CDCl_3$ solution at 25 °C, cycloreversion takes place and, in the case of **35**, the equilibrated system contains 4% of **1** with R = H and 14% with R = Ph, respectively (eq 15).[39,40]



(15)

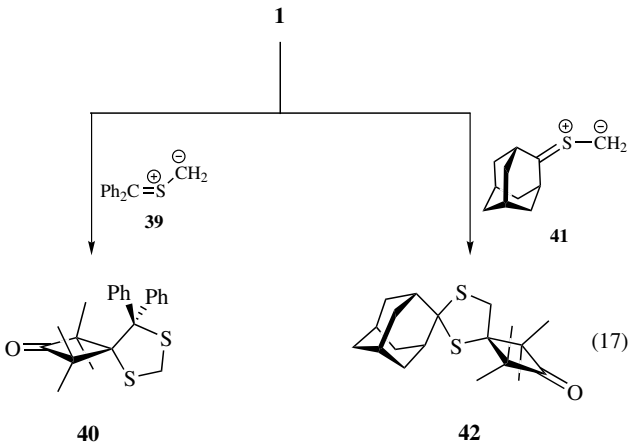
Azomethine Ylides. Various azomethine ylides, generated by different methods, can be trapped by **1** to give spirocyclic 1,3-thiazolidines. Thermolysis of *cis*-aziridines of type **37** in the presence of **1** occurs stereoselectively to give *trans*-configured cycloadducts (**38**) (eq 16).[41] Reactions carried out with *trans*-aziridines lead to *cis*-substituted 1,3-thiazolidines.



(16)

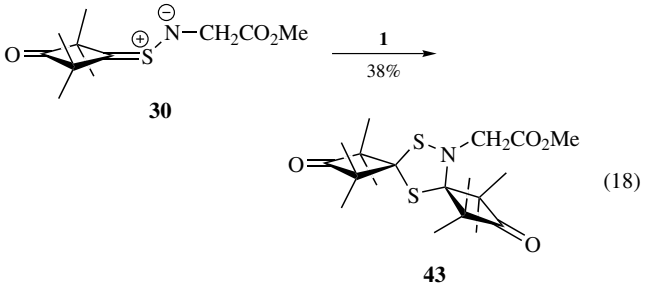
Using the desilylation methodology for the generation of azomethine ylides, 2,4-unsubstituted *N*-benzyl as well as *N*-unsubstituted 1,3-thiazolidines of type **38** are prepared.[42,43]

Thiocarbonyl Ylides. Thiocarbonyl ylides generated by thermolysis of 2,5-dihydro-1,3,4-thiadiazoles can be intercepted by **1** to give 1,3-dithiolane derivatives (so-called Schönberg products).[44] Both aromatic and cycloaliphatic *S*-methylides undergo [2+3]-cycloadditions with **1** regioselectively. Whereas **39** yields the sterically crowded adduct **40**,[45] adamantane *S*-methylide (**41**) affords the less hindered 1,3-dithiolane (**42**) (eq 17).[46] However, the reaction of **8**, the *S*-methylide of **1**, with thiobenzophenone results in a mixture of **40** and the opposite regioisomer.[45]



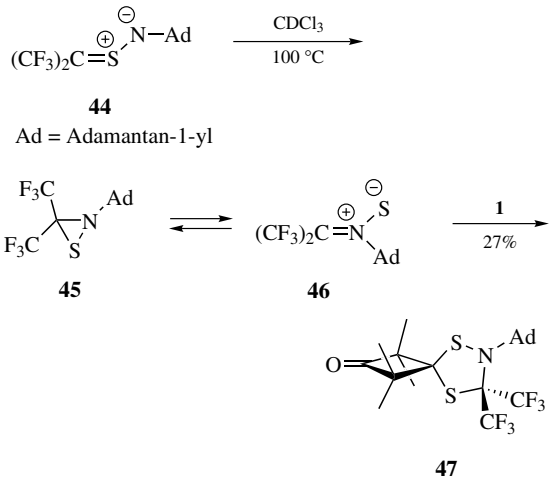
(17)

Thiocarbonyl S-Imides. In eq 13, the interception of a thiocarbonyl *S*-imide generated in situ from **1** and organic azides is outlined.[37] Similarly, thiocarbonyl *S*-imide (**30**, eq 14) undergoes a 1,3-dipolar cycloaddition with **1** in competition with the formation of the unstable thiaziridine **31**, and the corresponding 2,5-dispiro-1,4,2-dithiazolidine (**43**) and imine **32** are obtained (eq 18).[36] A similar reaction with methyl dithiobenzoate, in which along with 1,2,4-trithiolane (**34**) a 1,4,2-dithiazolidine of type **43** is formed, is also reported.[47]



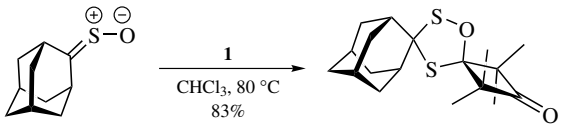
(18)

The stable, sterically crowded hexafluorothioacetone *S*-imide (**44**) reacts smoothly with aromatic thioketones, but the reaction with **1** requires elevated temperatures.[48,49] Unexpectedly, the product isolated after 3 h at 100 °C is 1,4,2-dithiazolidine (**47**). Its formation can be rationalized by the isomerization of **44** to give thiaziridine **45** being in an equilibrium with thionitrone **46**, which then traps **1** to yield **47** (eq 19).



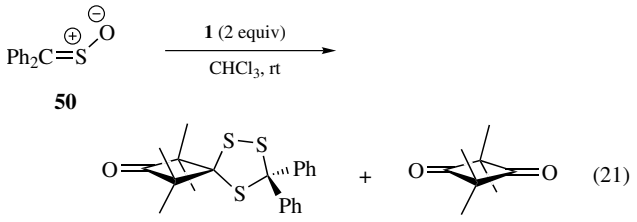
44 45 46 47 (19)

Thiocarbonyl S-Oxides (Sulfines). Cycloaliphatic sulfines such as **2** or **48** react with **1** in chloroform at 80 °C to give the stable 1,2,4-oxadithiolanes of type **49** in a regioselective [2 + 3] cycloaddition (eq 20).[50]



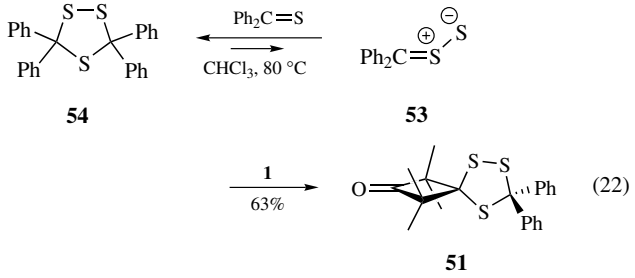
48 49 (20)

In contrast, the analogous cycloadducts of aromatic sulfines and **1** cannot be isolated. Instead, 1,2,4-trithiolane (**51**) is obtained in the reaction of thiobenzophenone *S*-oxide (**50**) with 2 equiv of **1** (eq 21).[51] In this multi-step reaction, a sulfur-transfer leading to a thiocarbonyl *S*-sulfide is proposed as a key step. The formation of equimolar amounts of 2,2,4,4-tetramethylcyclobutane-1,3-dione (**52**) indicates that in this system **1** acts as a sulfur donor. In a three-component system containing **50**, **1**, and (*E*)-cyclooctene, an episulfidation of the strained alkene is observed.[52]



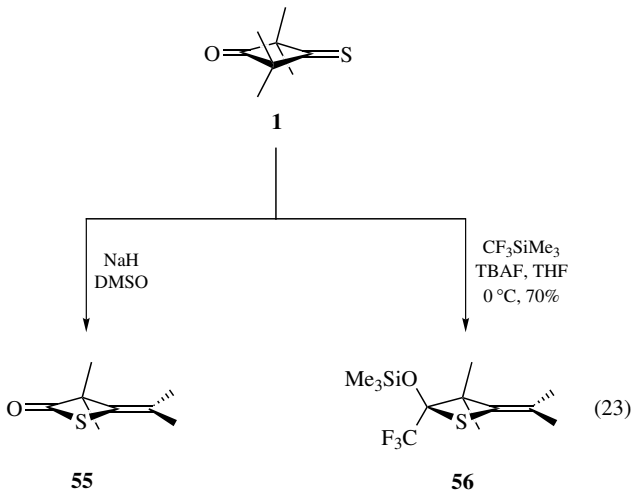
50 51 + 52 (21)

Thiocarbonyl S-Sulfides (Thiosulfines). The formation of the symmetrical 1,2,4-trithiolane (**34**, eq 14) is the evidence for the intermediacy of thiosulfine **33** formed by a sulfur transfer from thiaziridine **31** to **1**. The mixed 1,2,4-trithiolane (**51**) (eq 22) can result either from the [2 + 3]-cycloaddition of thiobenzophenone *S*-sulfide (**53**) with **1** or from **33** with thiobenzophenone. Both pathways are conceivable for the formation of **51** in a three-component reaction including **1**, thiobenzophenone, and phenyl azide.[53] Tetraphenyl-1,2,4-trithiolane (**54**) undergoes a [2 + 3]-cycloreversion and releases **53**, which is trapped by **1** to afford **51** (eq 22). The latter is stable under the reaction conditions.[51]



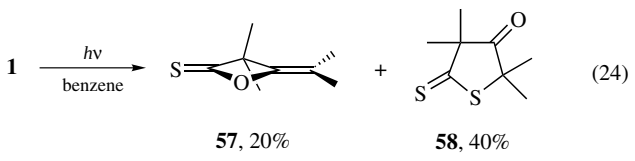
54 53 51 (22)

Isomerizations. The isomerization of **1** to thiolactone **55** occurs in DMSO solution in the presence of NaH.[2] It is reported that photolysis of **1** in methanol also affords **55**.[54] The reaction of **1** with (trifluoromethyl)trimethylsilane (Ruppert's reagent) in THF in the presence of fluoride yields the trifluoromethylated thietane **56** (eq 23).[55] A plausible mechanism of the transformation is a ring-opening/ring-closure process initiated by nucleophilic addition of trifluoromethanide to the carbonyl group of **1**.



55 56 (23)

Photolysis of **1** in benzene is reported to give another isomer with the structure **57** along with the ring-enlarged 3-oxodithiolactone (**58**) (eq 24).[56]

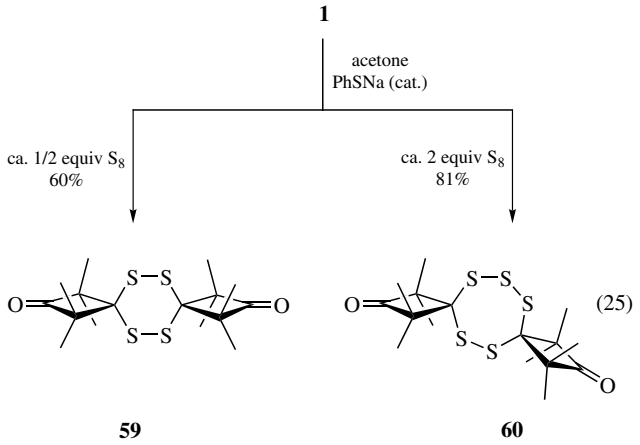


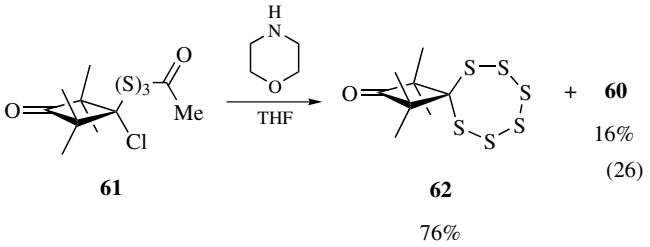
57, 20% **58**, 40% (24)

Miscellaneous. The sulfur-rich heterocycles **59** and **60** are produced when **1** in acetone is treated with elemental sulfur (S_8) in the presence of catalytic amounts of sodium thiophenolate (eq 25).[57] The type of the product depends on the ratio of **1** and S_8 used in the reaction.

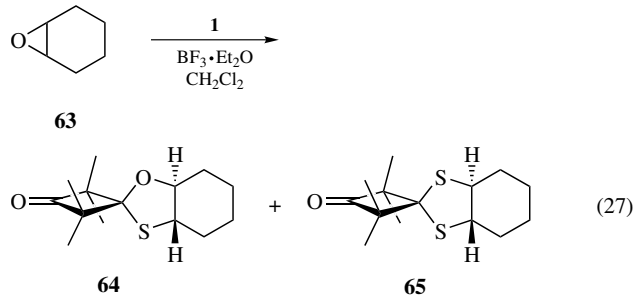
The related hexathiepane **62** can be prepared from the acetylated trisulfane **61**, obtained in two steps from **1**, by treatment with morpholine in THF solution (eq 26).[8]

Lewis acid-catalyzed reactions of **1** with oxiranes lead to 1,3-oxathiolanes and/or 1,3-dithiolanes. Whereas cyclohexene oxide (**63**) yields a mixture of **64** and **65**, only the corresponding 1,3-dithiolane is obtained in the case of cyclopentene oxide (eq 27).[58] The formation of 1,3-dithiolanes is evidenced to involve

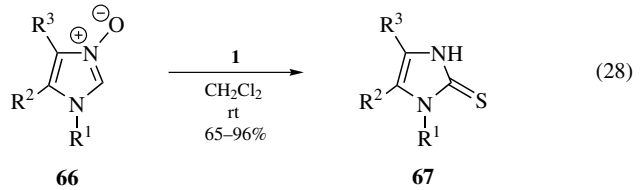




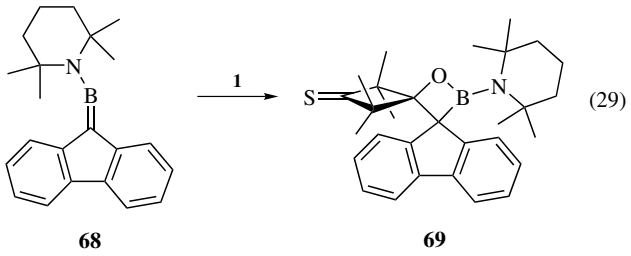
the correponding thiirane formed in situ by cleavage of the 1,3-oxathiolane ring. The structures of the products show that the heterocycle is formed with inversion of the configuration of one oxirane C-atom. This explanation is supported by the results obtained with **1** and *cis*- and *trans*-2,3-dimethyloxirane, respectively.[59] In this case, dispirocyclic 1:2 adducts are also formed by involvement of the carbonyl group of **1**.



A straightforward conversion of 2-unsubstituted imidazole 3-oxides (**66**) into the corresponding imidazole-2-thiones (**67**) is achieved by the reaction with **1** in dichloromethane at rt (eq 28).[60] This sulfur-transfer reaction can be applied to other azole *N*-oxides with an unsubstituted carbon atom next to the *N*-oxide position.



The reaction of amino-9-fluorenylideneborane (**68**) with **1** occurs chemo- and regioselectively at the carbonyl group to give the 1,2-oxaboretane (**69**) (eq 29).[61]



The irradiation of **1** in 2-propanol in the presence of oxygen at wavelengths > 400 nm results in the desulfurization of **1** to yield the parent dione **52**. Most likely, sulfur monoxide is a side product.[2]

1. Shirrell, C. D.; Williams, D. E., *Acta Crystallogr., Sect. B* **1974**, *30*, 1974.
2. Elam, E. U.; Davis, H. E., *J. Org. Chem.* **1967**, *32*, 1562.
3. Worman, J. J.; Shen, M.; Nichols, P. C., *Can. J. Chem.* **1972**, *50*, 3923.
4. Black, D. S. C.; Watson, K. G., *Aust. J. Chem.* **1973**, *26*, 2491.
5. Zwanenburg, B.; Wagenaar, A.; Thijs, L.; Strating, J., *J. Chem. Soc., Perkin Trans. 1* **1973**, 73.
6. Sundari, B.; Ramamurthy, V., *Indian J. Chem., Sect. B* **1984**, *23*, 498.
7. Koch, K. N.; Mloston, G.; Senning, A., *Eur. J. Org. Chem.* **1999**, 83.
8. Mloston, G.; Majchrzak, A.; Senning, A.; Søtofte, I., *J. Org. Chem.* **2002**, *67*, 5690.
9. Linden, A.; Majchrzak, A.; Cavegn, J.; Mloston, G.; Heimgartner, H., *Acta Crystallogr., Sect. C* **2002**, *58*, 480.
10. Masson, J.; Metzner, P.; Vialle, J., *Tetrahedron* **1977**, *33*, 3089.
11. Gassman, P. G.; Mullins, M. J., *Tetrahedron Lett.* **1980**, *21*, 2219.
12. Mloston, G.; Romanski, J.; Schmidt, C.; Reisenauer, H. P.; Maier, G., *Chem. Ber.* **1994**, *127*, 2527.
13. Mloston, G.; Romanski, J.; Swiatek, A.; Heimgartner, H., *Helv. Chim. Acta* **1999**, *82*, 946.
14. Mloston, G.; Romanski, J.; Heimgartner, H., *Heterocycles* **1999**, *50*, 403.
15. Huisgen, R.; Mloston, G.; Polborn, K.; Sustmann, R., *Chem. Eur. J.* **2003**, *9*, 2256.
16. Haiges, R., Ph.D. Thesis, University of Wuppertal, Germany, 2000; http://lpub.bib.uni-wuppertal.de/edoos/fachbereiche/09_chemie
17. Dawid, M.; Mloston, G.; Warkentin, J., *Chem. Eur. J.* **2002**, *8*, 2184.
18. Mloston, G.; Romanski, J.; Heimgartner, H., *Pol. J. Chem.* **2002**, *76*, 551.
19. Diebert, C. E., *J. Org. Chem.* **1970**, *35*, 1501.
20. Huisgen, R.; Penelle, J.; Mloston, G.; Buyle Padias, A.; Hall, H. K., *J. Am. Chem. Soc.* **1992**, *114*, 266.
21. Huisgen, R.; Mloston, G.; Fulka, C., *Heterocycles* **1985**, *23*, 2207.
22. Mloston, G.; Heimgartner, H., *Pol. J. Chem.* **2000**, *74*, 1503.
23. Mloston, G.; Heimgartner, H., In *The Chemistry of Heterocyclic Compounds, Vol. 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; Wiley: New York, 2002, p 315.
24. Huisgen, R.; Mloston, G.; Giera, H.; Langhals, E., *Tetrahedron* **2002**, *58*, 507.
25. Huisgen, R.; Mloston, G.; Langhals, E.; Oshima, T., *Helv. Chim. Acta* **2002**, *85*, 2668.
26. Huisgen, R.; Mloston, G.; Langhals, E., *Helv. Chim. Acta* **2001**, *84*, 1805.
27. Mloston, G.; Huisgen, R.; Giera, H., *Tetrahedron* **2002**, *58*, 4185.
28. Kägi, M.; Mloston, G.; Heimgartner, H., *Pol. J. Chem.* **1998**, *72*, 678.
29. Kägi, M.; Linden, A.; Mloston, G.; Heimgartner, H., *Helv. Chim. Acta* **1996**, *79*, 855.
30. Kägi, M.; Linden, A.; Mloston, G.; Heimgartner, H., *Helv. Chim. Acta* **1998**, *81*, 285.

31. Kelmendi, B.; Mloston, G.; Heimgartner, H., *Heterocycles* **2000**, *52*, 475.
32. Mloston, G.; Romanski, J.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta* **1996**, *79*, 1305.
33. Garratt, P. J.; Payne, D.; Tocher, D. A., *J. Org. Chem.* **1990**, *55*, 1909.
34. Freund, W.; Huenig, S., *J. Org. Chem.* **1987**, *52*, 2154.
35. Guziec, F. S.; Moustakis, C., *J. Chem. Soc., Chem. Commun.* **1984**, 63.
36. Mloston, G.; Romanski, J.; Linden, A.; Heimgartner, H., *Pol. J. Chem.* **1996**, *70*, 880.
37. Mloston, G.; Romanski, J.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta* **1993**, *76*, 2147.
38. Mloston, G.; Romanski, J.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta* **1995**, *78*, 1067.
39. Huisgen, R.; Fisera, L.; Giera, H.; Sustmann, R., *J. Am. Chem. Soc.* **1995**, *117*, 9671.
40. Giera, H.; Huisgen, R., *Liebigs Ann. Chem.* **1997**, 1685.
41. Mloston, G.; Urbaniak, K.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta* **2002**, *85*, 2644.
42. Gebert, A.; Linden, A.; Mloston, G.; Heimgartner, H., *Pol. J. Chem.* **2003**, *77*, 157.
43. Gebert, A.; Linden, A.; Mloston, G.; Heimgartner, H., *Pol. J. Chem.* **2003**, *77*, 867.
44. Mloston, G.; Huisgen, R., *Heterocycles* **1985**, *23*, 2201.
45. Huisgen, R.; Li, X.; Mloston, G.; Fulka, C., *Eur. J. Org. Chem.* **2000**, 1695.
46. Mloston, G.; Huisgen, R.; Polborn, K., *Tetrahedron* **1999**, *55*, 11475.
47. Mloston, G.; Romanski, J.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta* **1995**, *78*, 1499.
48. Mloston, G.; Celeda, M.; Roesky, H. W.; Parisini, E.; Ahlemann, J. T., *Eur. J. Org. Chem.* **1998**, 459.
49. Mloston, G.; Lesniak, S.; Linden, A.; Roesky, H. W., *Tetrahedron* **2000**, *56*, 4231.
50. Huisgen, R.; Mloston, G.; Polborn, K.; Sustmann, R.; Sicking, W., *Liebigs Ann. Chem.* **1997**, 179.
51. Huisgen, R.; Mloston, G.; Polborn, K.; Palacios-Gambra, F., *Liebigs Ann. Chem.* **1997**, 187.
52. Adam, W.; Bargon, R. M.; Mloston, G., *Eur. J. Org. Chem.* **2003**, 4012.
53. Mloston, G.; Heimgartner, H., *Helv. Chim. Acta* **1995**, *78*, 1298.
54. Muthuramu, K.; Ramamurthy, V., *Chem. Lett.* **1981**, 1261.
55. Mloston, G.; Prakash, G. K. S.; Olah, G. A.; Heimgartner, H., *Helv. Chim. Acta* **2002**, *85*, 1644.
56. Rao, N. B.; Chandrasekhar, J.; Ramamurthy, V., *J. Org. Chem.* **1988**, *53*, 745.
57. Huisgen, R.; Rapp, J.; Huber, H., *Liebigs Ann. Chem.* **1997**, 1517.
58. Blagoev, M.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta* **1999**, *82*, 2316.
59. Blagoev, M.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta* **2000**, *83*, 3163.
60. Mloston, G.; Gendek, T.; Heimgartner, H., *Helv. Chim. Acta* **1998**, *81*, 1585.
61. Channareddy, S.; Glaser, B.; Mayer, E. P.; Nöth, H.; Helm, S. W., *Chem. Ber.* **1993**, *126*, 1119.

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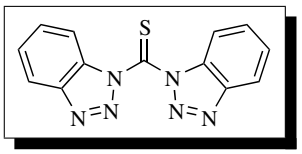
1,1′-(Thiocarbonyl)bis(1*H*-benzotriazole)



[4314-19-6] $C_{13}H_8N_6S$ (MW 280.31)

InChI = 1/C13H8N6S/c20-13(18-11-7-3-1-5-9(11)14-16-18)19-12-8-4-2-6-10(12)15-17-19/h1-8H

InChIKey = ZRXHYHZENMJKMG-UHFFFAOYAB

(thiocarbonyl transfer reagent for thiocarbamoylation of amines, phenols and thiols, dienophile for hetero-Diels–Alder reactions, one-carbon synthon for synthesis of guanidines, benzotriazolyl group donor)

Alternate Names: 1,1′-thiocarbonyldibenzotriazole, bis(benzotriazolyl)methanethione.

Physical Data: yellow needles; mp 176–178 °C,[1,2] 170–171 °C;[3] dipole moment 7.8 D.[4]

Solubility: sol dioxane, CH_2Cl_2, $CHCl_3$, hot acetone; insol benzene, THF, CCl_4.

Form Supplied in: Aldrich (yellow solid, 97% purity).

Analysis of Reagent Purity: ^{1}H (δ, $CDCl_3$): 7.56–7.61 (m, 2H), 7.70–7.75 (m, 2H), 8.20 (d, J = 8.3 Hz, 2H), 8.25 (d, J = 8.4 Hz, 2H); ^{13}C NMR (δ, $CDCl_3$): 113.9, 121.0, 126.9, 130.6, 133.0, 146.8, 169.6.

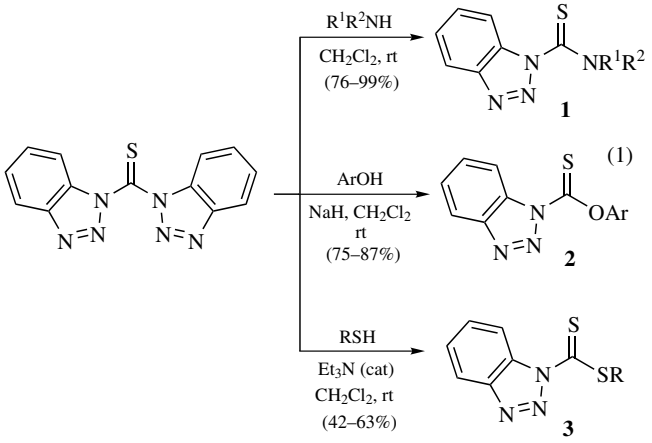
Preparative Methods: reaction of sodium salt of 1,2,3-benzotriazole[1,2] or 1-trimethylsilyl-1,2,3-benzotriazole[3] with thiophosgene. The latter approach is preferred due to the higher yield and purity of the product.

Purification: recrystallization from aqueous EtOH.

Handling, Storage, and Precautions: foul odor, can be stored for months in refrigerator, on storage at rt for a prolonged period slowly decomposes with color changing from yellow to green and then to brown, stable towards hydrolysis and methanolysis.[5]

Nucleophilic Substitution Reactions with Amines, Phenols and Thiols. 1,1′-Thiocarbonyldibenzotriazole serves as a valuable alternative to well-known thiocarbonyl transfer reagents, such as thiophosgene or 1,1′-thiocarbonyldiimidazole. Though 1,1′-thiocarbonyldibenzotriazole is generally less reactive than 1,1′-thiocarbonyldiimidazole, it is significantly less hygroscopic and more stable for storage at room temperature without loss of reactivity. At ambient temperature, 1,1′-thiocarbonyldibenzotriazole readily reacts with primary and secondary alkyl or heteroaryl amines,[6–8] phenols,[7] or thiols[7] with selective substitution of only one benzotriazolyl group affording intermediate 1-(thiocarbamoyl)- (**1**), 1-aryloxythiocarbonyl- (**2**), and 1-[(alkyl(aryl)thio) thiocarbonyl]-benzotriazoles (**3**), respectively (eq 1). Aliphatic alcohols are less reactive and afford the similar products in low yields, whereas reaction with primary arylamines is accompanied by elimination of the benzotriazole molecule and results in formation of aryl isothiocyanates.

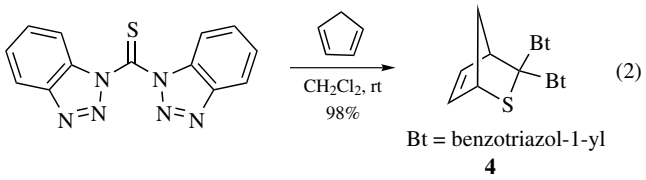
The second benzotriazolyl group in the intermediates obtained could be further substituted with a different primary or secondary amine, alcohol, thiol, or Grignard reagent to produce a variety of



(1)

unsymmetrical thioamides, thioureas, thiocarbamates, dithiocarbonates and thiocarbonates. The exception is *N*,*N*′-disubstituted 1-(thiocarbamoyl)benzotriazoles (**1**) (R^1, R^2, H), which are unreactive towards amines and alcohols.

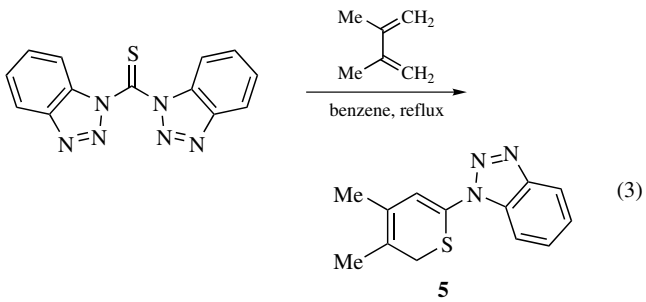
Hetero-Diels–Alder Cycloaddition with Dienes. Under mild conditions, 1,1′-thiocarbonyldibenzotriazole readily reacts with cyclopentadiene to afford the hetero-Diels–Alder cycloadduct (**4**) (eq 2) in 98% yield.[9] Analogous reaction with 2,3-dimethylbutadiene, carried out under harsher conditions, was accompanied with elimination of a benzotriazole molecule to give benzotriazolyl-substituted thiopyran (**5**) (eq 3).[10]



(2)

Bt = benzotriazol-1-yl

4

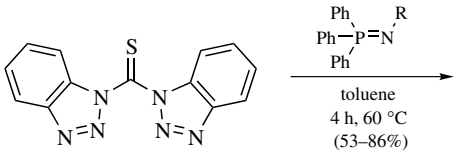


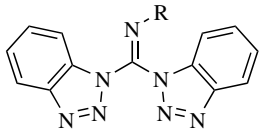
(3)

5

Imination with Triphenylphosphine Imides. Coupling of 1,1′-thiobisdibenzotriazole with triphenylphosphine imides occurs at the thiono group to afford bis(benzotriazolyl)-substituted carboximidamides **6** (eq 4) in moderate to high yields.[8] The benzotriazolyl groups in **6** could be readily substituted using primary amines or diamines to provide an access to a variety of functionalized guanidines. The analogous imination–substitution sequence can be carried out with the intermediates **1** (eq 1).

Benzotriazolation of Phosphates. Along with other benzotriazole reagents, such as 1,1′-carbonylbis(1*H*-benzotriazole) or 1,1′-sulfinylbis(1*H*-benzotriazole), 1,1′-thiocarbonyldibenzotriazole serves as a benzotriazolyl group donor in the reaction with AMP (eq 5).[11] The benzotriazolyl group in the phosphate **7** is readily substituted by phosphorylation with $Bu_3NH^+H_2PO_4^-$ to give ADP in 40–45% yield.

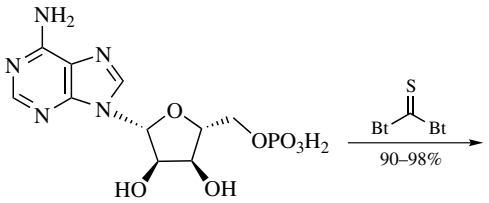




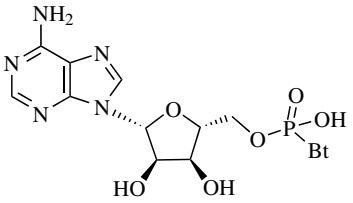
(4)

6

R = Ph, PhCO, 3-NCC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 4-$EtO_2CC_6H_4$



AMP



(5)

7

Bt = 1-benzotriazolyl

Related Reagents. Thiophosgene; 1,1′-Thiocarbonyldiimidazole.

1. Orth, R. E.; Soedigdo, S., *J. Heterocycl. Chem.* **1965**, *2*, 486.
2. Orth, R. E.; Soedigdo, S., *J. Pharm. Sci.* **1965**, *54*, 1702.
3. Larsen, C.; Steliou, K.; Harpp, D. N., *J. Org. Chem.* **1978**, *43*, 337.
4. Purygin, P. P.; Papchikhin, A. V., *Bull. Acad. Sci. USSR* **1983**, *32*, 1934.
5. Purygin, P. P.; Laletina, Z. P.; Sinitsina, N. K.; Shibaev, V. N., *Bull. Acad. Sci. USSR* **1983**, *32*, 1525.
6. Katritzky, A. R.; Ledoux, S.; Witek, R. M.; Nair, S. K., *J. Org. Chem.* **2004**, *69*, 2976.
7. Katritzky, A. R.; Witek, R. M.; Rodriguez-Garcia, V.; Mohapatra, P. P.; Rogers, J. W.; Cusido, J.; Abdel-Fattah, A. A. A.; Steel, P. J., *J. Org. Chem.* **2005**, *70*, 7866.
8. Katritzky, A. R.; Khashab, N. M.; Bobrov, S., *Helv. Chim. Acta* **2005**, *88*, 1664.
9. Larsen, C.; Harpp, D. N., *J. Org. Chem.* **1980**, *45*, 3713.
10. Harpp, D. N.; MacDonald, J. G.; Larsen, C., *Can. J. Chem.* **1985**, *63*, 951.
11. Purygin, P. P.; Kolodkina, I. I.; Kon'kova, E. P.; Yurkevich, A. M., *Khim.-Farm. Zh.* **1983**, *17*, 1235 (Chem. Abstr. *100*, 103797).

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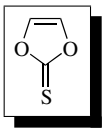
2-Thiono-1,3-dioxol-4-ene

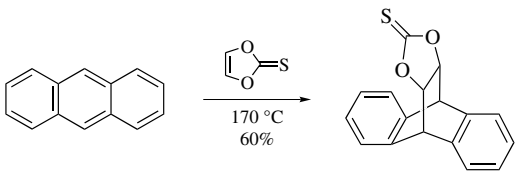


[37635-87-3] $C_3H_2O_2S$ (MW 102.12)
InChI = 1/C3H2O2S/c6-3-4-1-2-5-3/h1-2H
InChIKey = MMGCXSBBWCOBEX-UHFFFAOYAU

(dienophile in Diels–Alder reactions;[1] acetylene equivalent in cycloaddition reactions;[2] source of ketene;[3] forms dication dichalcogenides with strong Lewis acids[4])

Alternate Name: vinylene thionocarbonate.
Physical Data: mp 48 °C; bp 60–70 °C/0.2 mmHg.
Solubility: sol acetonitrile, benzene, carbon tetrachloride, dichloromethane, toluene; insol hexane.
Form Supplied in: not commercially available.
Preparative Method: prepared by reaction of phosphorus(V) sulfide with vinylene carbonate.[1]
Purification: recrystallization from benzene–hexane gives white crystals; sublimation at 120 °C generates long white needles.
Handling, Storage, and Precaution: material is apparently stable.

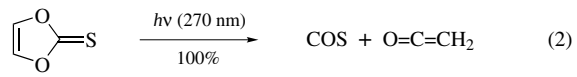
Cyclization with Dienes. The reaction of 2-thiono-1,3-dioxol-4-ene with anthracene at elevated temperatures leads to the production of the bicyclic adduct (**1**) (eq 1).[1,2] No other dienes have been reported to cyclize with this reagent. Diels–Alder adducts could be treated with phosphines to effect a Corey–Winter alkenation, which would render the reagent an acetylene equivalent.



(1)

(1)

Synthesis of Ketene. Photolysis (270 nm) of 2-thiono-1,3-dioxol-4-ene results in the quantitative formation of ketene via Wolff rearrangement of the corresponding α-ketocarbenes (eq 2).[3] Substituted dioxolenes can also be used in this fashion to generate substituted ketenes (eq 3). This serves as a convenient alternative to the use of α-diazo ketones in the generation of ketenes.



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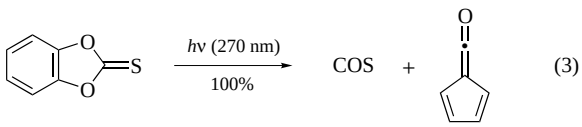
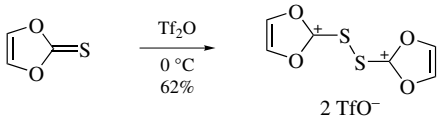


(3)

Preparation of Dication Dichalcogenides. Treatment of 2-thiono-1,3-dioxol-4-ene with trifluoromethanesulfonic anhydride leads to the formation of the corresponding dimeric dication (eq 4).[4] Hydrolysis of this stable dication with aqueous base generates equimolar amounts of both vinylene carbonate and vinylene thionocarbonate.[4]



(4)

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1. Fischer, H.-M.; Hartmann, W., *Chem. Ber.* **1972**, *105*, 2769.
2. Anderson, W. K.; Dewey, R. H., *J. Am. Chem. Soc.* **1973**, *95*, 7161.
3. Torres, M.; Clement, A.; Strausz, O. P., *J. Org. Chem.* **1980**, *45*, 2271.
4. Maas, G.; Singer, B., *Chem. Ber.* **1983**, *116*, 3659.

James W. Leahy
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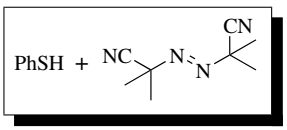
Thiophenol–Azobisisobutyronitrile



(PhSH)
[108-98-5] C_6H_6S (MW 110.19)
InChI = 1/C6H6S/c7-6-4-2-1-3-5-6/h1-5,7H
InChIKey = RMVRSNDYEFQCLF-UHFFFAOYAL
(AIBN)
[78-67-1] $C_8H_{12}N_4$ (MW 136.22)
InChI = 1/C8H12N4/c1-7(2,5-9)11-12-8(3,4)6-10/h1-4H3
InChIKey = OZAIFHULBGXAKX-UHFFFAOYAO

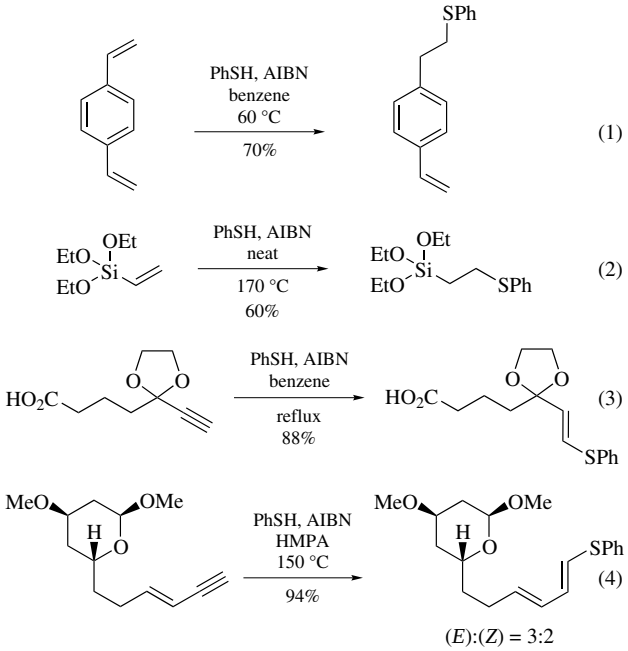
(preparation of benzenethiyl radicals with subsequent use in radical addition reactions of thiophenol to alkenes and alkynes;[1–4] alkene isomerizations[5])

Preparative Methods: prepared from thiophenol and azobisisobutyronitrile, both of which are commercially available.

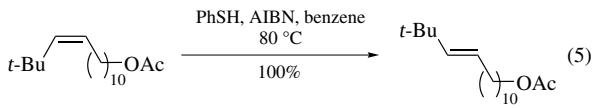
Synthesis of Sulfide Derivatives from Alkenes. Thermally induced decomposition of AIBN to cyanopropyl radicals initiates hydrogen abstraction from thiophenol in the title reagent system to give benzenethiyl radicals. Kinetic studies involving the addition of the thiol radical to 1,4-divinylbenzene (eq 1), using a catalytic amount of AIBN, demonstrate that the sulfide-containing styrene monomer can be prepared in high yield by carrying out the reaction at 60 °C with an equimolar ratio of thiophenol and the alkene.[1] More vigorous reaction conditions (170 °C) are necessary, however, in the thio radical addition to triethoxyvinylsilane (eq 2), since no reaction takes place even on prolonged heating at 100–110 °C.[2]

Synthesis of Vinyl Sulfides from Alkynes. The AIBN radical-initiated addition reaction of thiophenol to the terminal

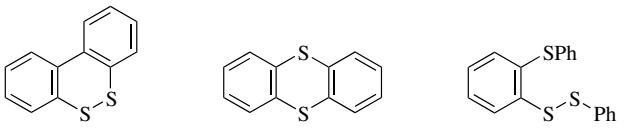
alkyne of a ynoic acid (eq 3) derivative provides the corresponding vinyl sulfide intermediate used in the synthesis of cyclohexanone derivatives.[3] This process has also been used in the synthesis of a chiral diene (eq 4) from an enyne precursor, a key intermediate in the enantiospecific total synthesis of (+)-compactin.[4]



Thiophenol-mediated Alkene Inversion. *trans*-Substituted alkenes containing a quarternary carbon center adjacent to the double bond are difficult to prepare by standard techniques, such as the Wittig reaction or by chemical reduction of the corresponding alkyne. However, they have been prepared by isomerizing the readily available *cis*-alkene using thiophenol–AIBN (eq 5).[5]



Heterocyclic Synthesis. The reaction of 1,2,3-benzothiadiazole with PhSH/AIBN in refluxing EtOAc provides a mixture of products including dibenzo[*c*,*e*]-*o*-dithiin (**1**), thianthrene (**2**), and 2-(phenylthio)diphenyl disulfide (**3**).[6]



(1) **(2)** **(3)**

1. Jiang, J.; Kobayashi, E.; Obata, T.; Furukawa, J., *Polym. J. (Tokyo)* **1990**, *22*, 963.
2. Seshadri, T.; Haupt, H. J., *Anal. Chem.* **1988**, *60*, 47.
3. Crich, K.; Eustace, K. A.; Fortt, S. M.; Ritchie, T. J., *Tetrahedron* **1990**, *46*, 2135.
4. Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J., *J. Am. Chem. Soc.* **1986**, *108*, 5908.
5. Schwarz, M.; Graminski, G. F.; Waters, R. M., *J. Org. Chem.* **1986**, *51*, 260.
6. Benati, L.; Montevecchi, P. C.; Tundo, A.; Zanardi, G., *J. Org. Chem.* **1976**, *41*, 1331.

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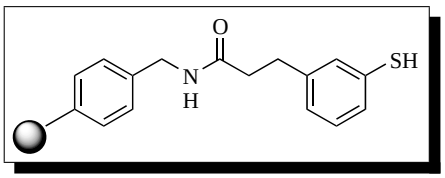
Thiophenol, Polymer-supported



Physical Data: loading 1.0–1.5 mmol g^{-1} (based on benzyl bromide uptake).

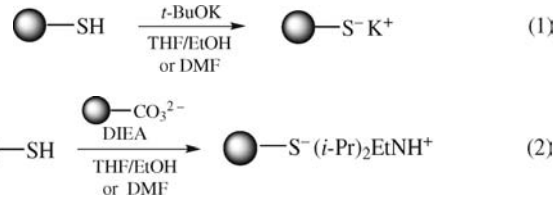
Solubility: 1% cross-linked polystyrene backbone is insoluble in all common aqueous and organic solvents.

Form Supplied in: yellow powder; bead size 75–150 μm, 100–200 mesh (95% within). Commercially available; retailer: Argonaut Technologies.[1]

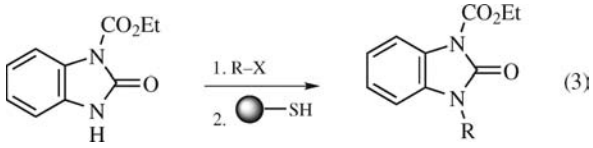
Purity: the polymer is washed in dichloromethane and dried in vacuo.

Handling, Storage, and Precaution: harmful if inhaled or ingested. Stable at room temperature.

Applications. Polymer-supported thiophenol (PS-thiophenol) has two principal applications in synthetic chemistry; it functions either as a scavenging agent or as a traceless solid-phase linker.[2] This functionalized polymer is commonly used as a phase transfer scavenger for a wide range of electrophiles including alkyl halides. It is easy to remove by filtration, thus enabling the preparation of products of high purity without the need for additional purification or isolation procedures. As with all scavenging procedures, 2 or 3 equiv of resin should be used to ensure complete removal of the surplus electrophile. The scavenging ability or nucleophilicity of PS-thiophenol has been found experimentally to be superior to the corresponding benzyl thiol attached to a polystyrene backbone.[1] Optimal scavenging results require either the formation of the potassium thiolate salt (formed using potassium trimethylsilylonate) (eq 1)[1] or the addition of diisopropylethylamine and mesoporous carbonate (eq 2).[1]

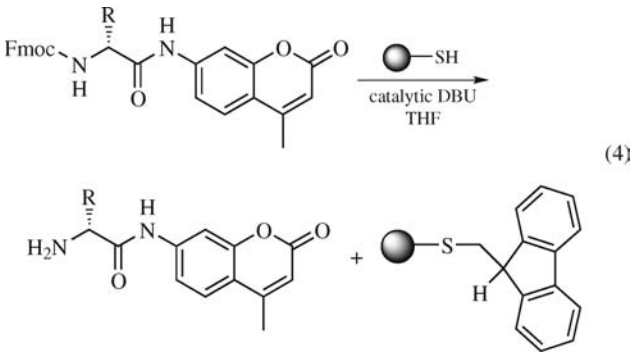


PS-thiophenol has been utilized in combinatorial library synthesis as an effective and clean method to remove excess electrophilic substrate[3] or alkylating reagent (eq 3).[4]



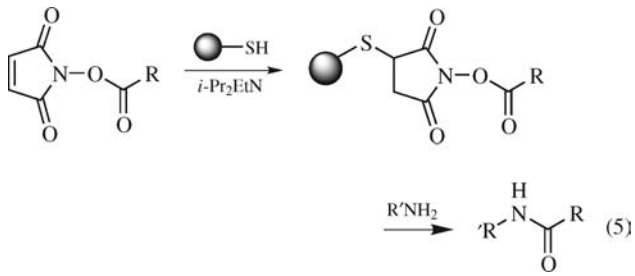
(3)

Another useful application of the resin involves amine deprotection reactions. PS-thiophenol/base can be used to remove the Fmoc protecting group and simultaneously capture the contaminating component (eq 4).[5]



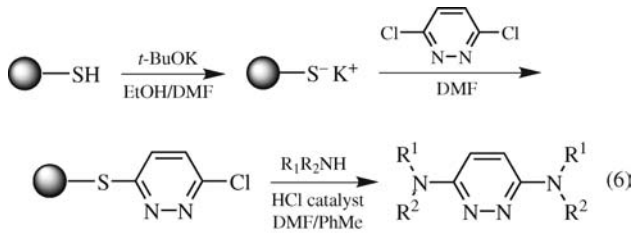
(4)

The reagent can also be used to attach suitable substrates, i.e. molecules susceptible to nucleophilic attack, onto the solid phase and thus facilitate a trivial purification procedure (eq 5).[6]



(5)

While attached to the resin, the isolated moiety can undergo further chemical manipulation with the PS-thiophenol acting as a linker moiety.[7] Cleavage is achieved by the addition of an amine (primary or secondary), causing nucleophilic displacement from the resin, which also results in additional modification of the molecule (eq 6). The functionalized polymer acts as a traceless linker without the need for oxidation to the sulfone or sulfoxide.



(6)

(R_2 = alkyl, aryl, H)

1. Catalog – Resins and Reagents. Argonaut Technologies, San Carlos, CA, USA, 2000.
2. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J., *J. Chem. Soc., Perkin Trans. 1* **2000**, *23* 3815.
3. Ley, S. V.; Massi, A., *J. Comb. Chem.* **2000**, *2*, 104.
4. Ermann, M.; Simkovsky, N. M.; Roberts, S. M.; Parry, D. M.; Baxter, A. D.; Montana, J. G., *Tetrahedron Lett.* **2000**, *41*, 2483.
5. Katoh, M.; Sodeoka, M., *Bioorg. Med. Chem. Lett.* **1999**, *9*, 881.
6. Parrot, I.; Wermuth, C.-G.; Hibert, M., *Tetrahedron Lett.* **1999**, *40*, 7975.
7. Sheppeck II, J. E.; Kar, H.; Hong, H., *Tetrahedron Lett.* **2000**, *41*, 5329.

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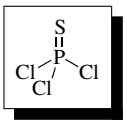
Thiophosphoryl Chloride

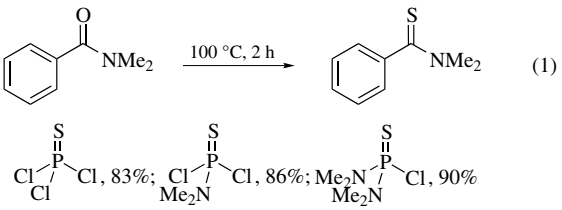


[3982-91-0] Cl_3PS (MW 169.39)
InChI = 1/Cl3PS/c1-4(2,3)5
InChIKey = WQYSXVGEZYESBR-UHFFFAOYAE

(thionation of amides; thiophosphorylating agent for alcohols, amines, diols, amino alcohols, diamines, etc.)

Physical Data: mp −35 °C; bp 125 °C; n_D 1.550; *d* 1.668 g cm^{-3}.
Solubility: sol benzene; CCl_4, $CHCl_3$, CS_2; reacts with alcohols and amines.
Form Supplied in: liquid; widely available.
Analysis of Reagent Purity: ^{31}P NMR.
Purification: distillation.[1]
Handling, Storage, and Precautions: highly toxic; corrosive, undergoes slow hydrolysis when exposed to moisture. Must handled in a fume hood and reactions performed under a dry, inert atmosphere.

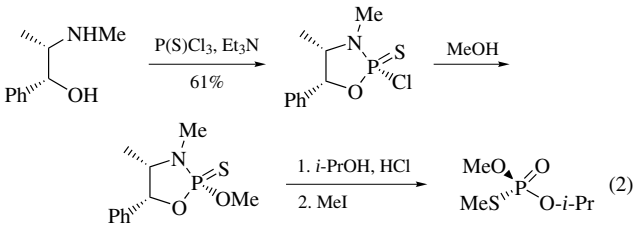
Thionation of Tertiary Amides.[2] Thiophosphoryl chloride and its *N,N*-dimethylamide derivatives (eq 1)[3] react with amides at elevated temperature to give thioamides in good yield. The reaction is run in an excess of the thiophosphorus compounds. The most efficient of the thionating agents examined is *N,N,N′,N′*-tetramethylamidophosphonothioic chloride.



(1)

Thiophosphorylation. Thiophosphoryl chloride will thiophosphorylate amines,[3] alcohols,[4] amino alcohols,[5] diols,[6] and diamines.[7] The rate of reaction decreases as each chlorine atom in replaced; thus it is possible to replace each chlorine atom with a different substituent under controlled reaction conditions. Thiophosphoryl derivatives of chiral amino alcohols have been studied extensively as stereochemical probes for the stepwise hydrolyses and alcoholysis of thiophosphates (eq 2), which can lead to the

formation of nonracemic chiral thiophosphates.[8] They have also been used as chiral derivatizing agents for the NMR analysis of chiral alcohols and amines.[9]



(2)

1. Moeller, T.; Birch, H. J.; Nielsen, N. C., *Inorg. Synth.* **1935**, *4*, 71.
2. Pedersen, B. S.; Lawesson, S. O., *Bull. Soc. Chim. Belg.* **1977**, *86*, 693.
3. Keat, R.; Shaw, R. A., *J. Chem. Soc.* **1965**, 4802.
4. Cremlyn, R. J. W.; Ellam, R. M.; Akhtar, N., *Phosphorus Sulfur Silicon* **1978**, *5*, 1.
5. Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Bajwa, G. S.; Burright, D. D.; Hutchinson, J. P., *J. Am. Chem. Soc.* **1986**, *108*, 6669.
6. Schultz, C.; Metschies, T.; Jastorff, B., *Tetrahedron Lett.* **1988**, *29*, 3919; Mikolajczyk, M.; Witczak, M.; Wieczorek, M.; Bokij, N. G.; Struchkov, Y. T., *J. Chem. Soc., Perkin Trans. 1* **1976**, 371.
7. Barluenga, J.; Jardon, J.; Palacios, F.; Gotor, V., *Synthesis* **1985**, 309; Cremlyn, R. J. W.; Frearson, J.; Milnes, D., *Phosphorus Sulfur Silicon* **1975**, *6*, 29.
8. Cooper, D. B.; Hall, C. R.; Harrison, J. M.; Inch, T. D., *J. Chem. Soc., Perkin Trans. 1* **1977**, 1969; Harrison, J. M.; Inch, T. D.; Lewis, G. J., *J. Chem. Soc., Perkin Trans. 1* **1975**, 1892; Harrison, J. M.; Inch, T. D.; Lewis, G. J.; Chittenden, R. A., *J. Chem. Soc., Chem. Commun.* **1975**, 720; Cooper, D. B.; Hall, C. R.; Inch, T. D., *J. Chem. Soc., Chem. Commun.* **1975**, 721.
9. Johnson, C. R.; Elliot, R. C.; Penning, T. D., *J. Am. Chem. Soc.* **1984**, *106*, 5019.

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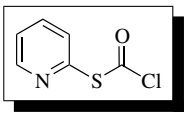
2-Thiopyridyl Chloroformate[1]



[73371-99-0] C_6H_4ClNOS (MW 173.63)
InChI = 1/C6H4ClNOS/c7-6(9)10-5-3-1-2-4-8-5/h1-4H
InChIKey = KAFAIALSGSIJFN-UHFFFAOYAE

(convenient preparation of 2-pyridylthiol esters;[2] subsequent transformation into lactones,[3] peptides,[4] and ketones[5])

Physical Data: ^{1}H NMR ($CDCl_3$) δ 8.64 m (1H), 7.75 m (2H), 7.38 m (1H).

Solubility: sol CH_2Cl_2, ether.

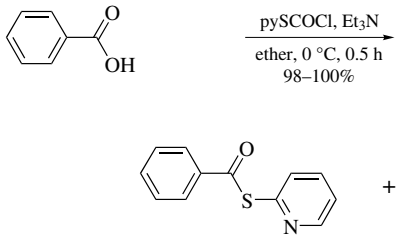
Form Supplied in: colorless oil; main impurity is bis(thiopyridyl) carbonate; not commercially available.

Analysis of Reagent Purity: IR (CH_2Cl_2) 1765 cm^{-1} (C=O); main impurity: IR (CH_2Cl_2) 1715 cm^{-1} (C=O).

Preparative Method: phosgene (5 equiv) in toluene and CH_2Cl_2 is cooled to 0 °C. Dropwise addition (5 min) of a CH_2Cl_2 solution of triethylamine (slight excess) and 2-pyridinethiol is followed by stirring for 10 min. After removal of excess phosgene and CH_2Cl_2 in vacuo, hexane is added and the resulting precipitate is filtered. After concentration of the combined filtrates, the colorless oil (96%) is dissolved in CH_2Cl_2 and stored at −25 °C.

Handling, Storage, and Precautions: very unstable to water and silica gel; however, it can be handled in air. It is stable for one month if stored at −25 °C. Since phosgene is used in preparing this reagent, preparation should be in a working fume hood and extreme caution is required.

Preparation of 2-Pyridylthiol Esters. 2-Pyridylthiol esters are formed by treating a carboxylic acid with 2-thiopyridyl chloroformate under extremely mild conditions (eq 1).[2] The $Et_3N\dot{c}HCl$ is removed by filtration or by washing with cold aqueous acid and base. After thorough drying, the thiol esters are generally pure enough to use in many synthetic applications.



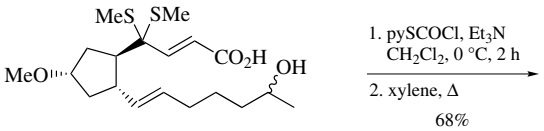
(1)

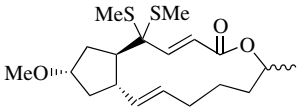
There are several other reagents for preparing 2-pyridylthiol esters. 1,3-dicyclohexylcarbodiimide[4] generally gives lower yields of the thiol ester and removal of the dicyclohexylurea can be difficult. Treating an acid chloride with thallium(I) 2-pyridinethiolate[6] has been used, but thallium salts are toxic. The method used most frequently before the introduction of 2-thiopyridyl chloroformate involves reacting a carboxylic acid with triphenylphosphine and 2,2′-dipyridyl disulfide.[7] This procedure suffers from the necessity of removing 2-pyridinethiol and triphenylphosphine oxide by chromatography, which precludes preparing large batches of the thiol esters since there can be a loss of product by reaction with the silica gel. 2-Thiopyridyl chloroformate provides access to many reported synthetic transformations. In some of these reports, the thiol ester has been prepared by other methods. However, use of 2-thiopyridyl chloroformate should make these transformations even more accessible.

Lactone Formation. There are several examples of the synthesis of lactones with 2-pyridylthiol esters.[3] Since this is a facile reaction, reasonable yields of complex macrocycles are obtained (eq 2).[8] The pyridine nitrogen may provide anchimeric assistance for the approaching nucleophile, thus facilitating the acylation.[3]

Ester Formation. 2-Pyridylthiol esters acylate lysophosphatidylcholines rapidly when catalyzed by silver ion, giving mixed-chain phosphatidylcholines in high yields and isomeric purity (eq 3).[9] The main advantages of this procedure over the usual 4-dimethylaminopyridine catalyzed acylation with acid anhydrides[10] are that less acylating reagent is required to give high

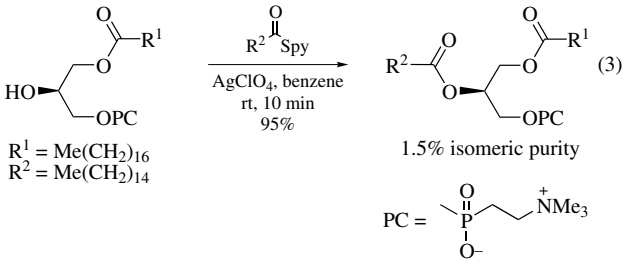
yields and rearrangement of the fatty acids is minimized. The main disadvantage is the sensitivity of the 2-pyridylthiol ester to water.





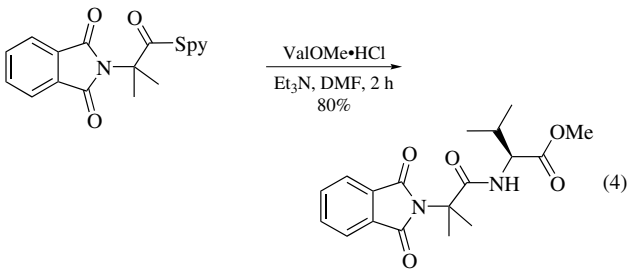
(2)

1:1 ratio of diastereomers



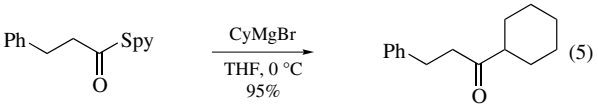
(3)

Peptide Coupling. These thiol esters have been used in the synthesis of several dipeptides. Many of the examples involve highly sterically hindered amino acids and result in very good yields and high optical purity (eq 4).[4] There are many useful active esters for peptide coupling, such as pentafluorophenol, *p*-nitrophenol, and *N*-hydroxysuccinimide. However, these do not work as well with the hindered amino acids shown in eq 4. Additionally, there are many direct coupling procedures; therefore the 2-pyridylthiol esters have not been used frequently.



(4)

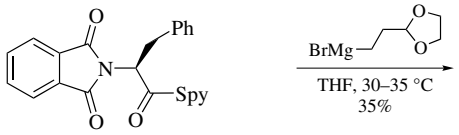
Ketones. Reaction of 2-pyridylthiol esters with Grignard reagents occurs rapidly to give ketones in almost quantitative yields (eq 5).[5] In all studies, less than 1% of the tertiary alcohol is observed. This procedure works reasonably well with a suitably protected amino acid to give the ketone (eq 6).[11] Phthaloyl protection of the amine is required since esters with amide NH groups decompose when treated with Grignard reagents.[11]

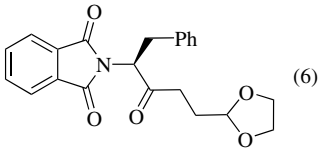


(5)

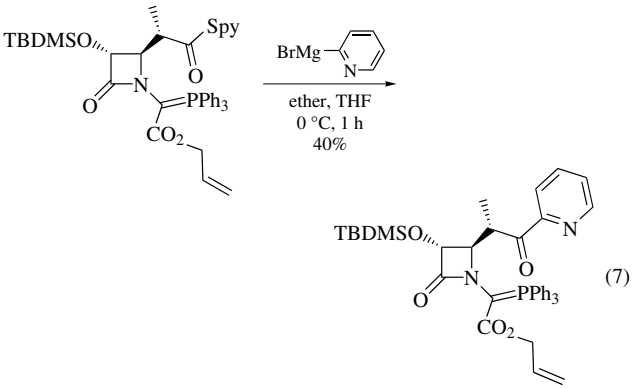
Preparation of thiol esters of highly elaborated phosphoranes with thiopyridyl chloroformate has been reported. Treatment of the thiol ester with an aryl Grignard reagent gives the corresponding ketone without epimerization of the chiral centers (eq 7).[12]

There are many procedures for reacting Grignard reagents with 'activated' carboxylic acids to give ketones. Other reagents used with varying degrees of success include acid chlorides, nitriles, acid anhydrides, and *N*-acylimidazolides (e.g. *N*,*N*′-carbonyldiimidazole, 1,1′-thionylimidazole).[13] Many of these give higher yields of the tertiary alcohol. However, treating acid chlorides with Grignard reagents at −78 °C gives better results,[14] so this may be an alternative to the thiol esters.





(6)



(7)

1. Haslam, E., *Tetrahedron* **1980**, *36*, 2409.
2. Corey, E. J.; Clark, D. A., *Tetrahedron Lett.* **1979**, *31*, 2875.
3. Corey, E. J.; Nicolaou, K. C., *J. Am. Chem. Soc.* **1974**, *96*, 5614.
4. Lloyd, K.; Young, G. T., *J. Chem. Soc. (C)* **1971**, 2890.
5. Mukaiyama, T.; Araki, M.; Takei, H., *J. Am. Chem. Soc.* **1973**, *95*, 4763.
6. Masamune, S.; Kamata, S.; Diakur, J.; Sugihara, Y.; Bates, G. S., *Can. J. Chem.* **1975**, *53*, 3693.
7. Mukaiyama, T.; Matsueda, R.; Suzuki, M., *Tetrahedron Lett.* **1970**, 1901.
8. Le Drian, C.; Greene, A. E., *J. Am. Chem. Soc.* **1982**, *104*, 5473.
9. Nicholas, A. W.; Khouri, L. G.; Ellington, J. C., Jr. Porter, N. A., *Lipids* **1983**, *18*, 434.
10. Gupta, C. M.; Radhakrishran, R.; Khorana, H. G., *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 4315.
11. Almquist, R. G.; Chao, W.-R.; Ellis, M. E.; Johnson, H. L., *J. Med. Chem.* **1980**, *23*, 1392.
12. Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G., *J. Med. Chem.* **1987**, *30*, 871.
13. (a) Shirley, D. A., *Org. React.* **1954**, *8*, 28. (b) Posner, G.; Witten, C. E., *Tetrahedron Lett.* **1970**, 4647. (c) Staab, H. A.; Jost, E., *Justus Liebigs Ann. Chem.* **1962**, *655*, 90.
14. Sato, F.; Inoue, M.; Oguro, K.; Sato, M., *Tetrahedron Lett.* **1979**, 4303.

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Thiourea Dioxide[1]

$NH_2C(=NH)SO_2H$

[1758-73-2] $CH_4N_2O_2S$ (MW 108.14)

InChI = 1/CH4N2O2S/c2-1(3)6(4)5/h(H3,2,3)(H,4,5)/f/h2,4H,3H2

InChIKey = FYOWZTWVYZOZSI-VAGMHOQLCS

(convenient and economical reducing agent for obtaining secondary alcohols from aliphatic,[2] alicyclic,[2] aromatic,[2] heterocyclic,[2] and steroidal ketones;[3] efficient reducing agent for the conversion of disulfides to thiols,[4] of *N*-tosylsulfilimines to sulfides,[4] of sulfoxides to sulfides,[5] and of halides and oxides of organotellurium and organoselenium to tellurides and selenides;[6] synthesis of substituted imidazoles[7])

Alternate Names: TUD; formamidinesulfinic acid; aminoiminomethanesulfinic acid.

Physical Data: mp 144 °C (dec).

Solubility: partially sol cold water; insol in organic solvents.

Preparative Method: prepared by oxidation of thiourea with hydrogen peroxide.[8]

Handling, Storage, and Precautions: moisture sensitive.

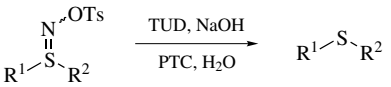
Reduction of Ketones to Secondary Alcohols.[2] A variety of ketones are reduced by TUD, in an aqueous ethanolic solution in the presence of NaOH, to the corresponding secondary alcohol in good yield. Generally, reduction of ketones requires 1–3 equiv of TUD and 2–6 equiv of NaOH; for example, dipropyl ketone gives heptan-4-ol (74%), benzophenone gives benzhydrol (100%), and 3-pyridyl phenyl ketone gives 3-pyridylphenylmethanol (100%). From the reaction mixture, almost theoretical amounts of the byproducts, sodium bisulfite and urea, are obtained.

Steroidal Ketones.[3] Using TUD, in the presence of an alkoxide in alcohol, steroidal ketones are reduced to the corresponding secondary alcohols. The reduction proceeds satisfactorily in the case of 3- and 6-keto steroids.[3] Steroidal diketones having a 20-oxo group do not undergo reduction with TUD. The results obtained from TUD, metal–alcohol (Bouveault–Blanc), and lithium aluminum hydride reductions are compared in Table 1. With all three reducing agents, 5α-cholestan-3-one gives the equatorial isomer as the major product. With 3β-hydroxy-5α-cholestan-3-one, TUD favors α-attack to produce predominantly the axial isomer.

Table 1 Comparison between TUD, metal–alcohol and $LiAlH_4$ reductions

		Yield (%)		
Substrate	Products	TUD	Na–ROH	$LiAlH_4$
5α-Cholestan-3-one	3α-ol	10	–	10
	3β-ol	90	100	90
3β-Hydroxy-5α-cholestan-6-one	3β,6α-diol	16	95	33
	3β,6β-diol	84	5	67

Reduction of Disulfides and of *N*-Tosylsulfilimines.[4] Disulfides and *N*-tosylsulfilimines are transformed into the corresponding thiols and sulfides (eq 1), respectively. For example, dibutyl disulfide is reduced to butanethiol (90%) and diphenyl disulfide to thiophenol (77%). The reactions are carried out under phase transfer conditions in the presence of a catalyst such as tributylhexadecylphosphonium bromide.



(1)

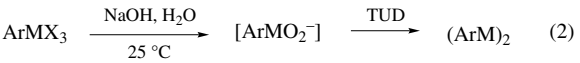
R^1	R^2	Yield (%)
Ph	Me	93
Bn	Me	68
Bn	Ph	83
Bn	Bn	67

Reduction of Sulfoxides.[5] Sulfoxides are reduced to the corresponding sulfides by TUD in the presence of iodine; for example, dibutyl sulfoxide gives dibutyl sulfide (89%) and diphenyl sulfoxide gives diphenyl sulfide (95%). The reaction is generally carried out by adding sulfoxides and iodine to a suspension of TUD in acetonitrile and then refluxing the mixture for a short time.

Reduction of Organoselenium and -tellurium Halides and Oxides.[6] TUD reduces aryltellurium trihalides to diaryl ditellurides (eq 2) and diorganyltellurium dihalides and telluroxides to diorganyl tellurides (eq 3) in high yield. The corresponding selenium compounds are reduced similarly. Some examples are given in Table 2. The reduction is performed by premixing the substrate and 2 N NaOH at room temperature for 15 min prior to the addition of TUD in petroleum ether.

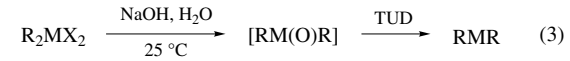
Table 2 Reduction of organotellurium and organoselenium halides and oxides by TUD

Starting material	Product	Yield (%)
$PhTeCl_3$	$(PhTe)_2$	92
$(C_{12}H_{25})_2TeCl_2$	$(C_{12}H_{25})_2Te$	86
PhTe(O)Bu	PhTeBu	77
$PhSeBr_3$	$(PhSe)_2$	93
Ph_2SeCl_2	PhSePh	92
Ph_2SeO	PhSePh	90



(2)

M = Te, Se

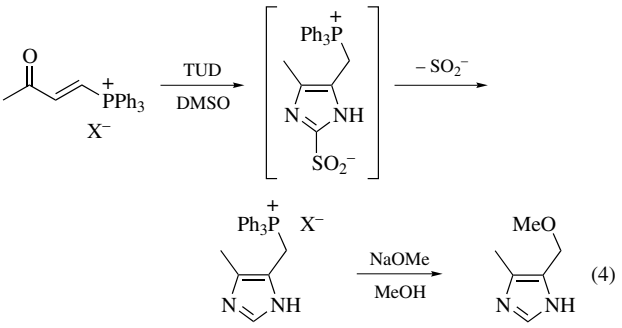


(3)

M = Te, Se

Reaction of Acylvinylphosphonium Halides with TUD.[7] Triphenyl-β-acetylvinylphosphonium halides (X = Cl, Br) react with TUD (in DMSO) in the presence of base (sodium hydride) to give the imidazolylphosphonium salts in high yield (eq 4). These imidazolyl halides can be readily converted to multifunctional imidazoles with quantitative recovery of PPh_3; for example, 4-methyl-(5-methylimidazolyl)triphenylphosphonium halide, on

treatment with NaOMe in MeOH, affords 5-methyl-4-methoxymethylimidazole.



(4)

1. *Fieser & Fieser* **1974**, *4*, 506; **1975**, *5*, 668; **1977**, *6*, 586.
2. Nakagawa, K.; Minami, K., *Tetrahedron Lett.* **1972**, 343.
3. Herz, J. E.; de Marquez, L. A., *J. Chem. Soc., Perkin Trans. 1* **1973**, 2633.
4. Borgogno, G.; Colonna, S.; Fornasier, R., *Synthesis* **1975**, 529.
5. Drabowicz, J.; Mikolajczyk, M., *Synthesis* **1978**, 542.
6. Lang, E. S.; Comasseto, J. V., *Synth. Commun.* **1988**, *18*, 301.
7. Webb, R. L.; Lewis, J. J., *J. Heterocycl. Chem.* **1981**, *18*, 1301.
8. de Barry Barnett, E., *J. Chem. Soc* **1910**, *97*, 63.

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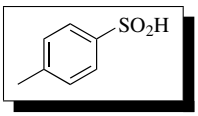
p-Toluenesulfinic Acid



[536-57-2] $C_7H_8O_2S$ (MW 156.22)
InChI = 1/C7H8O2S/c1-6-2-4-7(5-3-6)10(8)9/h2-5H,1H3,(H,8,9)/f/h8H
InChIKey = FXJVNINSOKCNJP-FZOZFQFYCV
(Na salt·H_2O)
[824-79-3] $C_7H_9O_3NaS$ (MW 196.22)
InChI = 1/C7H8O2S.Na.H2O/c1-6-2-4-7(5-3-6)10(8)9;;/h2-5H,1H3,(H,8,9);;1H2/q;+1;/p-1/fC7H7O2S.Na.H2O/q-1;m;
InChIKey = WUHWAOGAJFMIFU-VZCYFQKICG

(preparation of alkyl, vinyl, and allyl sulfones; starting material for the preparation of chiral sulfoxides; mild acid catalyst)

Physical Data: mp 85 °C; pK_a 1.66. The sodium salt hydrate has mp >300 °C.[1]

Solubility: sol ethanol, ether; sparingly sol water, hot benzene.

Form Supplied in: commercially available as the sodium salt hydrate; the lithium salt *[16844-27-2]* is also available.

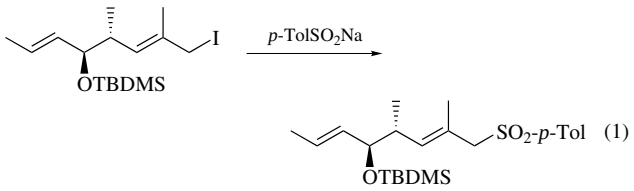
Preparative Methods: isolation of the free acid via acidification of an aqueous solution of the sodium salt has been described;[1b] partial conversion to *p*-toluenesulfonic acid frequently accompanies drying of the free acid.

Purification: recrystallizes in water in long rhombic needles or plates.

Handling, Storage, and Precautions: should be stored in a cool, dry place away from strong oxidizing agents.

Synthesis of Sulfones. *p*-Toluenesulfinic acid is a frequently used reagent for the synthesis of organic sulfones. The sulfone group has played an extensive role in recent synthetic organic chemistry; some of its common applications are described below, following preparation of representative sulfones from the title reagent. Unless otherwise noted, the reactions described use the sodium salt rather than the free acid.

Alkylation of arenesulfinate salts is a very general reaction for the preparation of alkyl sulfones.[2] Reaction conditions utilizing alcoholic or dipolar aprotic solvents are typical, but phase-transfer conditions have been described.[3] Reaction with reactive halides is generally facile (eq 1);[4] triflates have likewise been displaced with ease by *p*-toluenesulfinate.[5]



(1)

The sulfones so obtained are useful in a variety of organic transformations. Alkyl sulfones are readily deprotonated with bases, and the resulting carbanions are good nucleophiles. Sulfones thus function as activating groups which can subsequently be removed under mild conditions.[6] Alkylation of alkyl sulfones by alkyl halides, followed by reductive cleavage with lithium metal or sodium amalgam, provides a method of coupling alkyl halides which has been useful in the synthesis of 1,4-dienes.[7] Sodium *p*-toluenesulfinate also undergoes conjugate addition reactions[8] and has been used as a nucleophile in palladium-catalyzed substitution reactions of allylic substrates.[9]

The addition of sulfone-substituted anions to carbonyl compounds yields β-hydroxy sulfones. These are useful intermediates for the synthesis of unsaturated compounds via elimination processes.[10–13] β-Hydroxy sulfones may also be prepared via the regioselective ring opening of epoxides by sodium *p*-toluenesulfinate.[14]

The radical addition of sulfinates to unsaturated compounds via the iodosulfonylation–dehydroiodination[15] reaction sequence constitutes a general method for the preparation of vinyl sulfones; the latter may be rearranged to allylic sulfones by treatment with base.[16] The radical addition may be carried out on α,β-unsaturated carbonyl compounds as well as alkenes.[17] In the case of unsaturated carbonyl compounds the elimination process can be quite stereoselective, (*E*)-alkenes being normally formed. For the addition to nonconjugated alkenes, conditions have been described for the preparation of either (*E*)- or (*Z*)-alkenes.[16]

Cleavage of Vinylsilanes. *p*-Toluenesulfinic acid has been used for the protodesilylation of vinylsilanes to provide alkenes.[18] This method is milder than the usual strong acids used for this purpose. The cleavage is not stereospecific.

Synthesis of Chiral Sulfoxides. Chiral sulfoxides have been used extensively in asymmetric synthesis.[19] An extremely

common method for the preparation of these compounds involves the reaction of resolved diastereomeric sulfinate esters with Grignard reagents and organolithium species.[20] Menthol has classically been used to form diastereomeric esters of *p*-toluenesulfinic acid; an improved method using sulfinate esters of *trans*-2-phenylcyclohexanol has recently been reported.[21]

1. (a) *Dictionary of Organic Compounds*, 5th ed., Third Supplement; Chapman and Hall: New York, 1985; p 292. (b) *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 11th ed.; Budavari, S., Ed.; Merck: Rahway, NJ, 1989; p 1501.
2. Meek, J. S.; Fowler, J. S., *J. Org. Chem.* **1968**, *33*, 3422.
3. Crandall, J. K.; Pradat, C., *J. Org. Chem.* **1985**, *50*, 1327.
4. Cox, C. M.; Whiting, D. A., *J. Chem. Soc., Perkin Trans. 1* **1991**, 1901.
5. Tanner, D.; Somfai, P., *Tetrahedron* **1987**, *43*, 4395.
6. For reviews, see (a) Durst, T. In *Comprehensive Organic Chemistry*; Barton, D. H. R.; Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, p 171. (b) Magnus, P. D., *Tetrahedron* **1977**, *33*, 2019.
7. Grieco, P. A.; Masaki, Y., *J. Org. Chem.* **1974**, *39*, 2135.
8. Sánchez, I. H.; Aguilar, M. A., *Synthesis* **1981**, 55.
9. Safi, M.; Sinou, D., *Tetrahedron Lett.* **1991**, *32*, 2025.
10. Julia, M.; Paris, J. M., *Tetrahedron Lett.* **1973**, 4833.
11. Otera, J.; Misawa, H.; Sugimoto, K., *J. Org. Chem.* **1986**, *51*, 3830.
12. Kocienski, P. J.; Lythogue, B.; Ruston, S. J., *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.
13. Achmatowicz, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J.; Wicha, J., *Tetrahedron* **1988**, *44*, 4989.
14. Biswas, G. K.; Bhattacharyya, P., *Synth. Commun.* **1991**, 569.
15. Barluenga, J.; Martinez-Gallo, J. M.; Nájera, C.; Fañanás, F. J.; Yus, M., *J. Chem. Soc., Perkin Trans. 1* **1987**, 2605.
16. Kobayashi, T.; Tanaka, Y.; Ohtani, T.; Kinoshita, H.; Inomata, K.; Kotake, H., *Chem. Lett.* **1987**, 1209.
17. Nájera, C.; Baldó, B.; Yus, M., *J. Chem. Soc., Perkin Trans. 1* **1988**, 1029.
18. Büchi, G.; Wüest, H., *Tetrahedron Lett.* **1977**, 4305.
19. (a) Solladié, G., *Synthesis* **1981**, 185. (b) Posner, G. H., *Acc. Chem. Res.* **1987**, *20*, 72.
20. (a) Solladié, G.; Hutt, J.; Girardin, A., *Synthesis* **1987**, 173. (b) Hulce, M.; Mallamo, J. P.; Frye, L. L.; Kogan, T. P.; Posner, G. H., *Org. Synth.* **1986**, *64*, 196; *Org. Synth., Coll. Vol.* **1990**, *7*, 495.
21. Whitesell, J. K.; Wong, M.-S., *J. Org. Chem.* **1991**, *56*, 4552.

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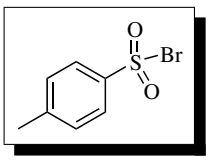
p-Toluenesulfonyl Bromide



[1950-69-2] $C_7H_7BrO_2S$ (MW 235.10)
InChI = 1/C7H7BrO2S/c1-6-2-4-7(5-3-6)11(8,9)10/h2-5H,1H3
InChIKey = NTSFJZORNYYLFW-UHFFFAOYAK

(reagent used as a radical cyclization initiator and sulfonating, halogenating reagent)

Alternate Name: 4-methylbenzenesulfonyl bromide, tosyl bromide, TsBr.

Physical Data: mp 95–96 °C.

Solubility: sparingly soluble in H_2O; soluble in toluene, benzene, and methylene chloride.

Form Supplied in: solid, not commercially available.

Analysis of Reagent Purity: melting point; a detailed structural analysis was performed using electron diffraction, MS,[1] and IR.[2]

Preparative Methods: the title reagent can be prepared by the following methods: treatment of tosylsulfonic acid anhydride with HBr in AcOH for 20–30 min;[3] reacting *p*-toluenesulfonylhydrazide with a mixture of NaBr and $NaBrO_3$ in acidic solution;[4] reacting *p*-toluenesulfonylhydrazide with 2 mol of bromine;[5] diazotizing *p*-aminotoluene in 48% HBr at 3 °C with solid $NaNO_2$ then adding to a mixture of SO_2, benzene, $CuBr_2$, and KBr in dioxane;[6] and reacting the sodium salt of *p*-toluenesulfinic acid with bromine.[7]

Purity: recrystallization from low boiling pet. ether.[4]

Handling, Storage, and Precaution: not available, but should be similar to tosyl chloride.

General Discussion. Various kinetic and reactivity studies have been performed using TsBr alone or in comparison with other arene sulfonyl halides.[8,9] Most of the literature describes the use of this reagent to initiate free radical ring formation, predominantly for five-membered ring systems. There are, however, reports of its use in vinyl sulfone and thiolsulfonate formation and in halogenation reactions.

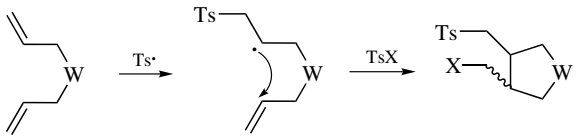
Reactions with Free Radicals. The basis of the use of TsBr in radical reactions is the facile formation of the tosyl radical from the initiator AIBN or light. da Silva Correa reported a comparative study of the decomposition of AIBN in the presence of TsBr and TsI and proposed tosyl radical formation as follows (eq 1).

$$\text{AIBN} \xrightarrow{\text{heat}} N_2 + 2Me_2\dot{C}\,CN$$

$$Me_2\dot{C}CN + TsBr \longrightarrow Me_2C(CN)Br + p\text{-}MeC_6H_4\dot{S}O_2 \quad (1)$$

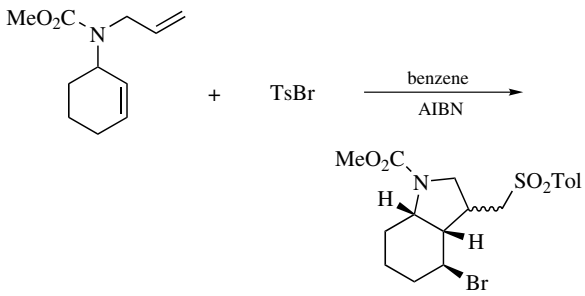
In the absence of an olefinic co-reactant, the tosyl radical undergoes disproportionation and, to a lesser extent, dimerization. According to the study, about 30% of the Me_2CCN radicals are involved in bromine abstraction from TsBr and about 50% of them are involved in iodine abstraction from TsI, illustrating the useful productivity of tosyl radical generation by this method.[10] In another study, da Silva Correa's group reported the relative rates of halogen extraction (by phenyl radical) as I:Br:Cl = 602:192:1.[11]This would seem to discourage the use of tosyl chloride in this free radical manifold, however, the two reports demonstrate that useful yields of cyclized products can be obtained by employing different radical initiators (vide infra).[12,13] The consequences of the relative reactivity difference are illustrated in a number of comparative studies of TsBr vs TsI as detailed below.

Radical Cyclization Reactions. The capable radical chain carrying character of tosyl bromide has been applied to the cyclization of several 1,6-dienes. In many examples, the products result from addition of the tosyl radical to the terminus of the less-substituted olefin, followed by 5-*exo-trig* cyclization with the second olefin to deliver a five-membered ring product. In all cases, *cis*-stereochemistry predominates. In some cases, however, the 1,2-addition of tosyl bromide to one olefin is the observed product. The generic reaction sequence is pictured below (eq 2).



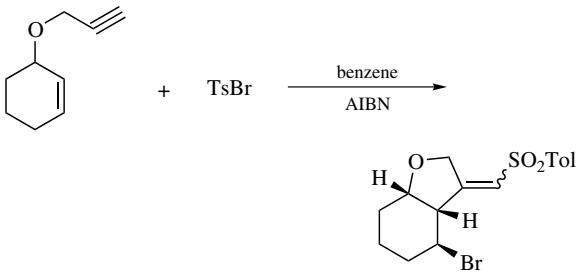
(2)

Reaction outcomes have been reported for 1,6-hexadiene (W=CH_2, X=Br, I),[15] diallyl sulfide (W=S, X=Br, I),[14] diallyl ether (W=O, X=Br,[12,15,16] I[15,16]), diallyl sulfone (W=SO_2, X=Br, I),[15] diallylmalonates [W=$C(CO_2R)_2$, X=Cl,[13] Br,[17,18]], diallyl sulfonamide (W=N-Ts, X=Cl, Br),[12] and diallyl carboxyamide (W=N-CO_2R, X=Cl,[13] Br,[16]). Changing the steric and electronic character of the olefins can influence the regiochemical outcome in these systems. Less-substituted olefins (eq 3),[16] electron-rich acetylenes (eq 4),[16] and allenes (eq 5)[19] react preferentially. Bis-allenic[20] and 1,6-diyne systems[21] also undergo radical cyclization. These factors are exemplified below.



(3)

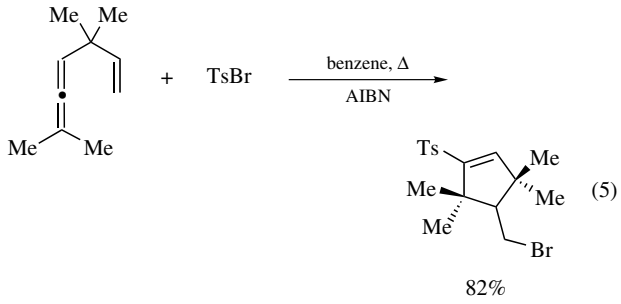
90%
~1.2:1 ratio



(4)

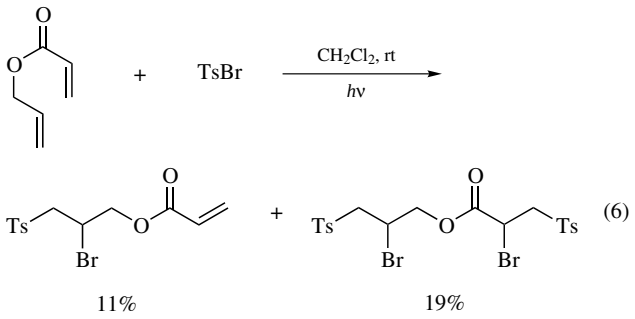
43%
~4:1 (*Z*:*E*)

Although allylic acrylates are reported to give 1,2-addition without cyclization (eq 6),[14,15] allylic acrylamides do successfully cyclize (eq 7).[13]



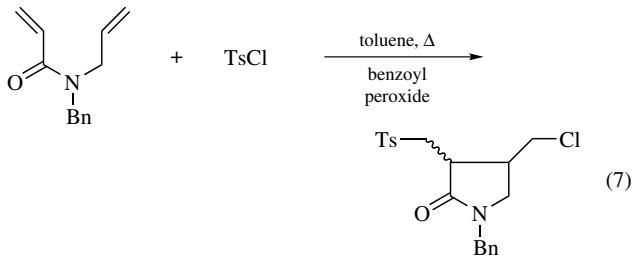
(5)

82%



(6)

11% 19%

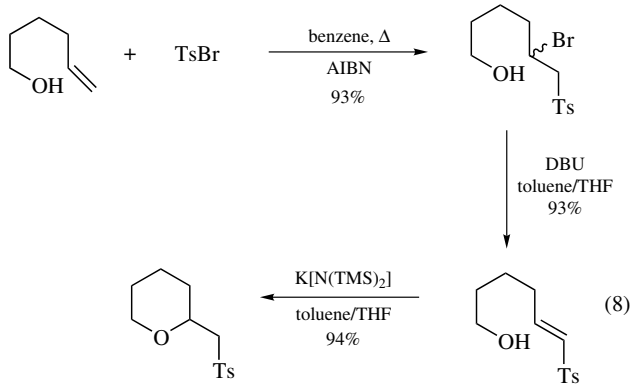


(7)

64%
4:1 (*cis*:*trans*)

Radical Additions to Olefins. Edwards, Craig, and Muldoon reported an approach to tetrahydropyrans through the intramolecular conjugate addition of an alcohol to a vinyl sulfone, formed by the addition and subsequent dehydrohalogenation of tosyl bromide (and iodide) to an appropriately positioned olefin (eq 8). [22]

Kang et al. reported that the radical addition of tosyl bromide (and iodide) to allenic alcohols produced the tosyl-substituted, bromo allylic alcohols or cyclic ethers (eq 9).



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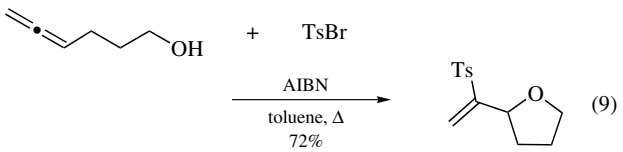

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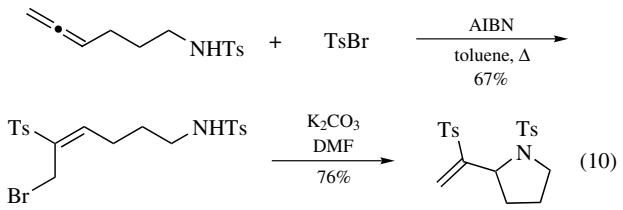
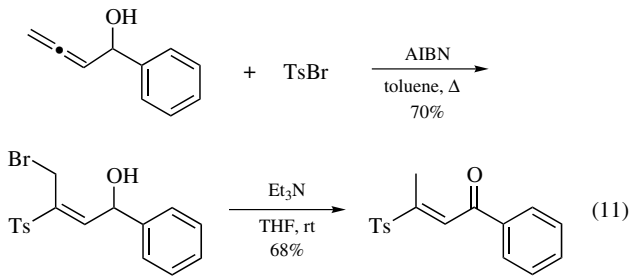
The similar addition to allenic tosyl sulfonamides produced the bromo allylic sulfonamides which were cyclized with potassium carbonate in DMF (eq 10).[23]



(10)

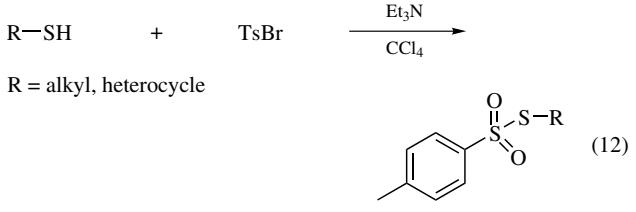
Extending this work to α-allenic alcohols, Kang demonstrated the synthesis of β-tosyl-substituted-α,β-unsaturated ketones (eq 11).[24]



(11)

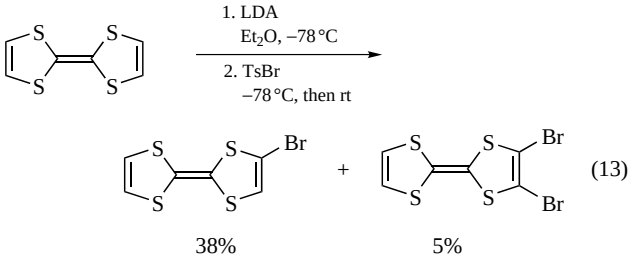
Preparation of Thiolsulfonates. Fuchs and Ranasinghe demonstrated that mercaptans, in the presence of triethylamine, rapidly reacted with tosyl bromide to produce good yields of the mixed thiolsulfonates (eq 12).[25] This reaction stands in stark contrast to the analogous reaction with tosyl chloride which simply yields the disulfide.

This work was subsequently extended to other benzene thiols[26] and to 6- and 7-mercapto-2-aminobenzothiazoles which cleanly underwent the conversion to the mixed thiolsulfonates, with pyridine as the base, with no observed formation of sulfonamide from competing sulfonylation of the 2-amino group.[27]



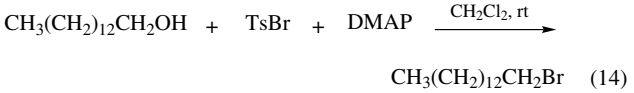
(12)

Halogenation. A few examples in the literature report the use of TsBr as a halogenating reagent. Bryce and Cooke were able to brominate tetrathiafulvalene in fair yield by reaction with LDA at −78 °C followed by treatment with TsBr (eq 13).[28]



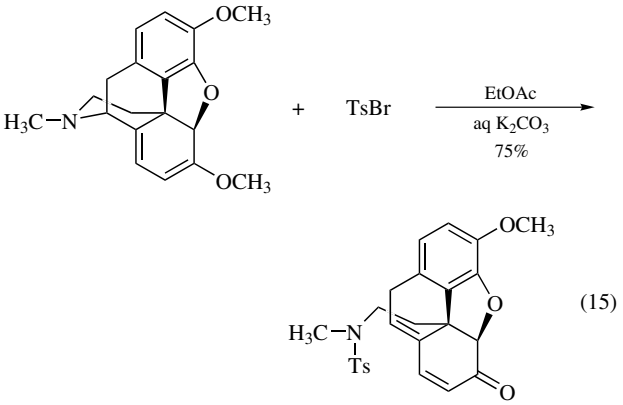
(13)

Nicolaou has reported a one-step conversion of hydroxyl groups to bromides which appears general (eq 14).[29]



(14)

Miscellaneous. In an interesting example of the enhanced reactivity of this reagent (in comparison with tosyl chloride), Fuchs reported the ring opening of thebaine with tosyl bromide under standard Schotten–Baumann acylation conditions (eq 15).[30]



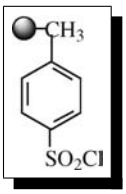
(15)

1. Petrov, V. M.; Petrova, V. N.; Kislov, V. V.; Ivanov, S. N.; Noskov, S. Yu.; Krasnov, A. V.; Bylova, Z. M., *J. Struct. Chem.* **2000**, *41*(6), 939.
2. Kozhevina, L. I.; Makarova, R. A.; Rybachenko, V. I.; Titov, E. V., *Zh. Prikladnoi Spektroskopii* **1982**, *36*(4), 63643 (AN **1982**, 207678).
3. Lukashevich, V. O., *Dokl. Akad. Nauk SSSR* **1955**, *103*, 627 (AN **1956**, 27746).
4. Poshkus, A. C.; Herweh, J. E.; Magnotta, F. A., *J. Org. Chem.* **1963**, *28*(10), 2766.
5. Litvinenko, L. M.; Dadali, V. A.; Savelova, V. A.; Krichevtsova, T. I., *Zh. Obshch. Khim.* **1964**, *34*(11), 3730 (AN **1965**, 36574).
6. Prinsen, A. J.; Cerfontain, H., *Rec. Trav. Chim. Pays-Bas* **1965**, *84*(1), 24.
7. Whitmore, F. G.; Thurman, N., *J. Am. Chem. Soc.* **1923**, *45*, 1068.
8. Gnedin, B. G.; Ivanov, S. N.; Spryskov, A. A., *Zh. Org. Khim.* **1976**, *12*(9), 1939 (AN **1977**, 43014).
9. Popov, A. F.; Sadovskii, Yu. S.; Solomoichenko, T. N.; Piskunova, Zh. P.; Savelova, V. A.; Lobanova, O. V.; Nduvimana, M., *Russ. J. Org. Chem.* **1999**, *35*(12), 1831.
10. da Silva Correa, C. M. M.; Oliveira, M. A. B. C. S., *J. Chem. Soc., Perkin Trans. 2* **1987**, 811.
11. da Silva Correa, C. M. M.; Oliveira, M. A. B. C. S., *J. Chem. Soc., Perkin Trans. 2* **1983**, 711.
12. Bertrand, M. P.; De Riggi, I.; Surzur, J. M., *Tetrahedron* **1988**, *44*(23), 7119.

13. Chuang, C.-P.; Ngoi, T. H. J., *Tetrahedron Lett.* **1989**, *30*(46), 6369.
14. da Silva Correa, C. M. M.; Serra, A. C.; Vieira, M. A. M. S. A.; Gomes, M. A., *Tetrahedron* **1990**, *46*(8), 3061.
15. da Silva Correa, C. M. M.; Serra, A. C.; do Vale, M. L. C., *Tetrahedron* **1991**, *47*(45), 9463.
16. Simpkins, N. S.; Brumwell, J. E.; Terrett, N. K., *Tetrahedron* **1994**, *50*(47), 13533.
17. Bertrand, M. P.; De Riggi, I.; Surzur, J.-M.; Archavlis, A.; Faure, R., *Tetrahedron* **1990**, *46*(15), 5285.
18. Bertrand, M.; Jaime, C.; De Riggi, I.; Nouguier, R.; Surzur, J. M.; Lesueur, C.; Virgili, A., *Bull. Soc. Chim. Fr.* **1993**, *130*, 229.
19. Hatem, M. J.; Gueddari, F. E.; Grimaldi, J. R., *Tetrahedron Lett.* **1995**, *36*(37), 6685.
20. Kang, S.-K.; Ha, Y.-H.; Kim, D.-H.; Lim, Y.; Jung, J., *Chem. Commun. (Cambridge)* **2001**, *14*, 1306.
21. Caddick, S.; Shering, C. L.; Wadman, S. N., *Chem. Commun. (Cambridge)* **1997**, *2*, 171.
22. Edwards, G. L.; Craig, D. C.; Muldoon, C. A., *Synlett* **1997**, *11*, 1318.
23. Kang, S.-K.; Ko, B.-S.; Ha, Y.-H., *J. Org. Chem.* **2001**, *66*, 3630.
24. Kang, S.-K.; Ko, B.-S.; Lee, D.-M., *Synth. Commun.* **2002**, *32*(21), 3263.
25. Fuchs, P. L.; Ranasinghe, M. G., *Synth. Commun.* **1988**, *18*(3), 227.
26. Prasad, J. V. N. V.; Boyer, F. E.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hagen, S. E.; Markoski, L. J.; Tait, B. D.; Lunney, E. A.; Tummino, P. J.; Ferguson, D.; Holler, T.; Hupe, D.; Nouhan, C.; Gracheck, S. J.; VanderRoest, J. S.; Saunders, J.; Iyer, K.; Sinz, M.; Brodfuehrer, J., *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1481.
27. Prasad, J. V. N. V.; Panapoulous, A.; Rubin, J. R., *Tetrahedron Lett.* **2000**, *41*, 4065.
28. Bryce, M. R.; Cooke, G., *Synthesis* **1991**, *4*, 263.
29. Nicolaou, K. C.; Hwang, C. K.; Li, W. S., *Tetrahedron Lett.* **1984**, *25*(22), 2295.
30. Fuchs, P. L.; Toth, J. E., *J. Org. Chem.* **1986**, *51*(13), 2594.

John E. Toth & Elizabeth A. Collins
Eli Lilly and Company, Indianapolis, IN, USA

p-Toluenesulfonyl Chloride and Related Reagents, Polymer-supported



[941-55-9]

(solid support for organic synthesis and immobilized reagents and catalysts, and solid-phase scavenger of nucleophiles)

Alternate Name: polymer-supported tosyl chloride, PS-TsCl, PS-SO_2Cl.

Solubility: compatible with CH_2Cl_2, THF, DMF, and other swelling solvents.

Form Supplied in: cream to off-white powder.

Preparative Methods: commercially available; prepared from sulfonated ion exchange resins (e.g., Dowex) via chlorination[1] or divinylbenzene-crosslinked polystyrene resin via chlorosulfonation.[1]

Handling, Storage, and Precaution: small particles are dangerous if inhaled; very small particles may pass through the skin and mucous membranes. Store in a cool (<60 °C), dry place. Do not tightly pack dry resin in glass containers, as swelling may cause glass to shatter when resin is exposed to solvents. Rapid build-up of pressure may occur if resin is used in conjunction with strong oxidizing agents.

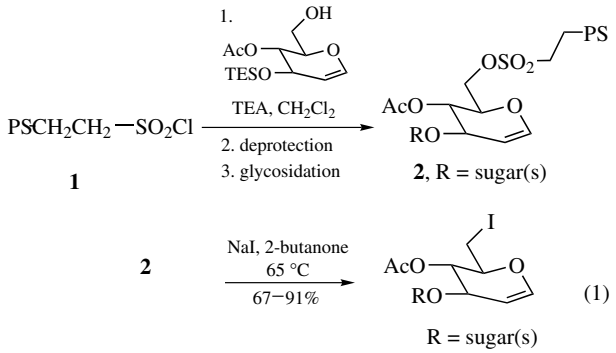
Introduction. Polymer-supported sulfonyl chlorides (PS-SO_2Cl) have been used as supports for solid-phase organic synthesis, as solid-phase scavengers of nucleophiles, and as supports for immobilized reagents and catalysts.[2] Like the analogous solution-phase reagents *p*-toluenesulfonyl chloride and methanesulfonyl chloride, PS-SO_2Cl resins react readily with a wide variety of nucleophiles. The resulting sulfonyl-nucleophile bonds can generally be cleaved under conditions similar to those used in the solution phase. The PS-SO_2Cl resins offer various advantages over the solution-phase reagents: ease of purification of the resin-bound molecules by filtration and washing, reduced toxicity and odor (the PS-SO_2Cl resins are not lachrymators), and ease of adaptation for use in automated synthesis.

A polymer-supported *p*-toluenesulfonyl chloride is commercially available from Argonaut; this resin will herein be referred to as PS-TsCl. The Argonaut Technologies website (http://www.argotech.com) provides extensive information about their PS-TsCl resin, including sample procedures, literature references, and an MSDS. Other PS-SO_2Cl resins have been synthesized from a variety of solid supports, including polystyrene, Dowex, Merrifield's resin, and the Wang resin (see below for examples and references). Unless a particularly low loading, or a particularly long linker proves necessary, the reactions performed on these synthesized resins should be translatable to the commercially available PS-TsCl.

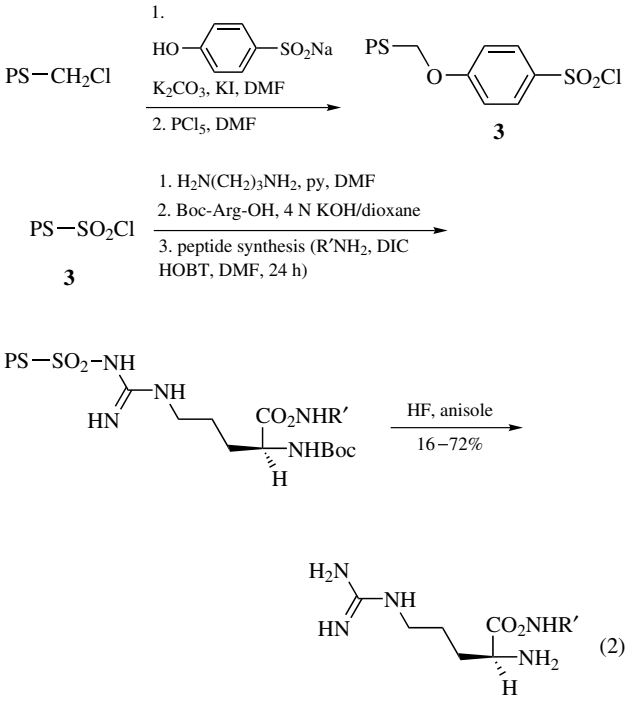
Traceless and Activating Linker for Solid-phase Synthesis. PS-SO_2Cl resins have been used as polymeric supports for the solid-phase synthesis of a wide variety of compounds, including oligosaccharides, peptides, and small organic molecules. The sulfonyl linker on these resins has commonly been called 'traceless' because the entire sulfonyl moiety remains connected to the solid support upon nucleophilic or reductive cleavage; however, in the context of this review, the term 'traceless' is applied only to examples in which the point of attachment to the resin is replaced with a hydrogen upon cleavage. The PS-SO_2Cl sulfonyl linker has also served as an activating moiety to promote the efficiency and selectivity of various solid-phase reactions.

Solid-phase Oligosaccharide Synthesis. Methanesulfonyl chloride resin **1** was used as an activating linker in the synthesis of various polymer-bound di and trisaccharides **2** (eq 1).[3] The sulfonate linker proved stable to glycosidation and alcohol deprotection conditions, and nucleophilic displacement of **2** by NaI provided 6-iodosaccharides (eq 1). NaOAc and NaN_3 were also suitable nucleophiles for cleavage of the sulfonate linker.[3]

A sulfonate linker has also been used to immobilize a glucose derivative on a Multipin™ system for potential use in the preparation of oligosaccharide libraries.[4]

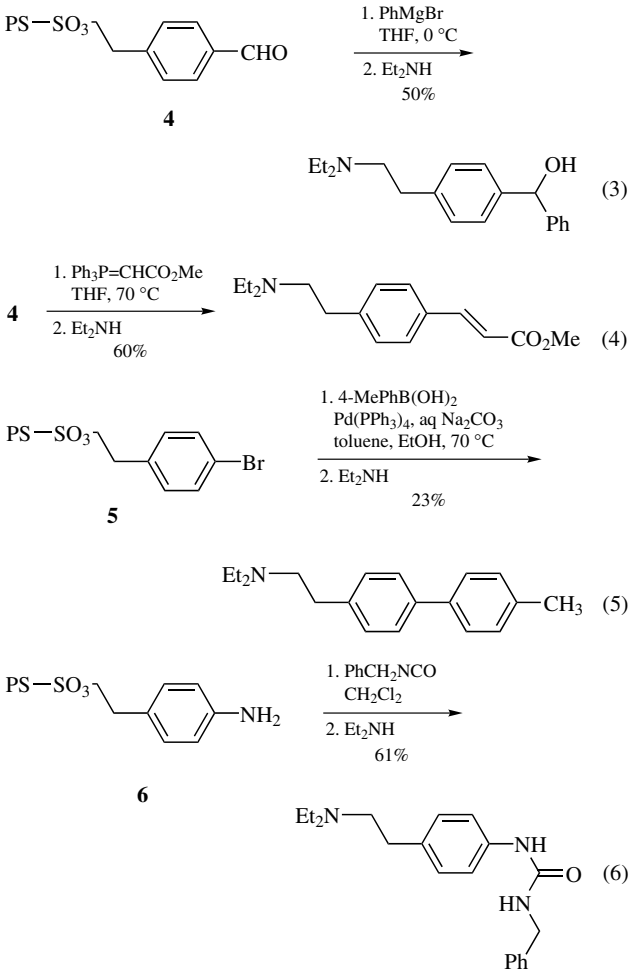


Solid-phase Peptide Synthesis. *p*-Alkoxyphenylsulfonyl chloride resin **3** was developed for the traceless solid-phase synthesis of arginine-containing peptides.[5] The guanidine moiety of arginine was anchored onto resin **3**, which served as both a solid support and a guanidine protecting group; di, tri, tetra, and hexapeptides were synthesized on this solid support (eq 2). The sulfonamide linker proved compatible with both Boc and Fmoc peptide chemistry, and was cleaved tracelessly with anhydrous HF.

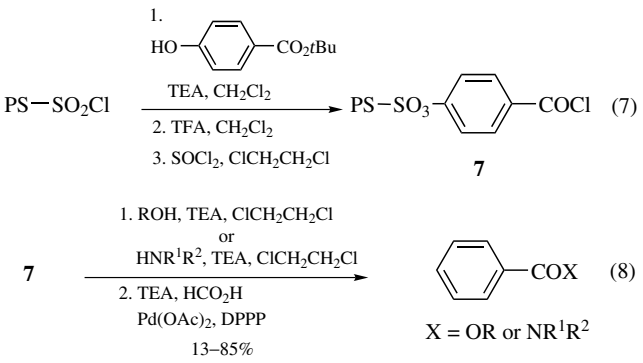


Solid-phase Organic Synthesis. Functionalized resins **4**–**6** were prepared from *p*-alkoxyphenylsulfonyl chloride resin **3**, and the sulfonate linker in these resins was shown to be stable under a variety of reaction conditions.[6] Aldehyde resin **4** underwent addition of Grignard reagents (eq 3) and a Wittig reagent (eq 4), as well as reduction with $NaBH_4$, and reductive amination with various amines.[6]

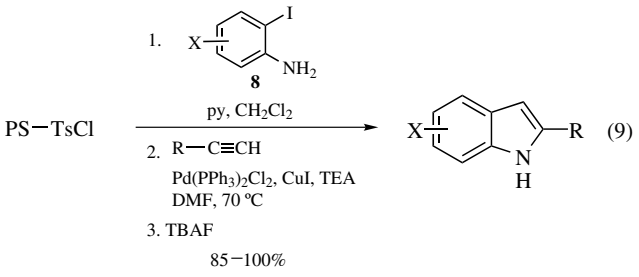
Bromide resin **5** underwent Suzuki coupling (eq 5), and amine resin **6** reacted with isocyanates (eq 6), acid chlorides, and a sulfonyl chloride.[6] All resin-bound products were cleaved by displacement of the sulfonate linker with diethylamine in 23–>95% isolated yield, and in ca. 90% purity.[6]



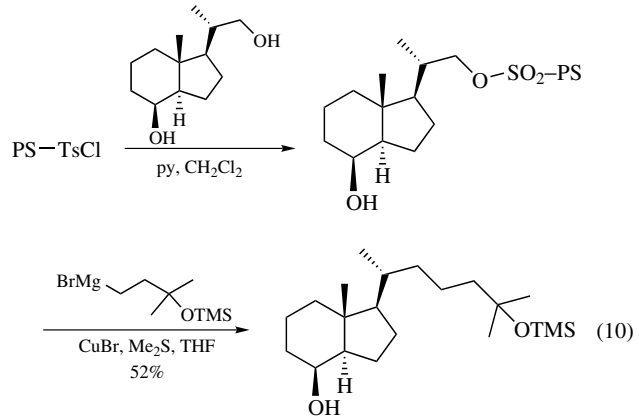
The benzoyl chloride–functionalized resin **7** was prepared in three steps (eq 7) from a toluenesulfonyl chloride resin (prepared, in turn, by chlorination of Dowex 50W ion-exchange resin).[7] Resin **7** was coupled with a variety of alcohols and amines to afford the corresponding resin-bound benzoate esters and benzamides, which were tracelessly cleaved under Pd^0-catalyzed reductive conditions in 13–85% yields (eq 8).[7]



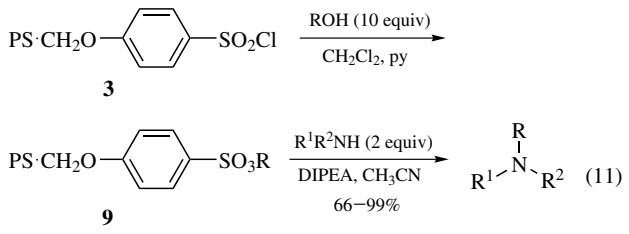
PS-TsCl was used in the solid-phase synthesis of indoles.[8] Loading of anilines **8** onto PS-TsCl was followed by Sonogashira coupling (eq 9). The coupled products cyclized under the reaction conditions to provide the corresponding indoles; this cyclization was promoted by the electron-withdrawing sulfonyl linker.[8] Traceless cleavage of the sulfonyl linker with TBAF provided the indoles in 85–100% yield.



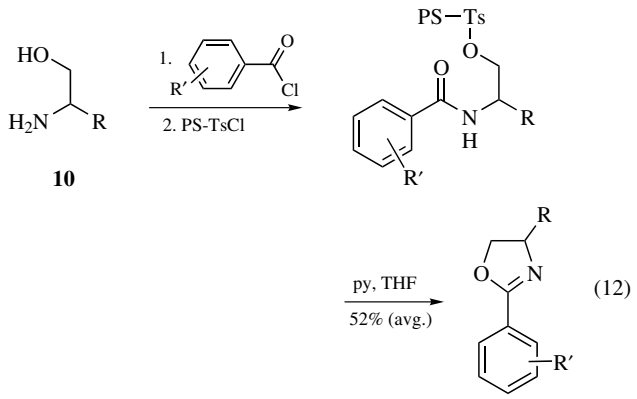
PS-TsCl was also used in an exploration of a solid-phase synthesis of a vitamin D library (eq 10).[9] The resin was shown to be compatible with oxidation reactions using either the Dess-Martin reagent or PDC. Simultaneous alkylation and cleavage of the sulfonate linker by a copper-catalyzed Grignard reaction proceeded in 52% isolated yield (eq 10). The PS-TsCl resin proved too sterically congested for the library synthesis; however, a sulfonate linker strategy was eventually pursued with a different solid support.[9]



Catch-and-release Synthesis. Catch-and-release synthesis is a special case of solid-phase synthesis in which a small molecule is first immobilized on the solid support, then simultaneously transformed and released from the resin by reaction with a solution-phase reagent. PS-SO_2Cl resin **3** has been used in catch-and-release synthesis for the transformation of alcohols to secondary amines (eq 11), sulfides, and alkylated imidazoles via sulfonate resin **9**.[10]

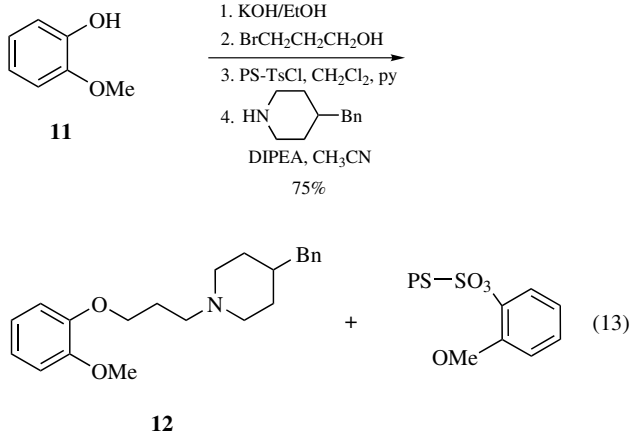


An example of intramolecular ring-forming release is shown in eq 12.[11] Amino alcohols **10** were *N*-acylated with acid chlorides and the crude product was loaded onto PS-TsCl. Base-promoted, ring-forming displacement of the tosylate released the oxazolines into solution. Ring-forming release of a sulfonate linker has also been utilized with a Multipin™ system.[12]



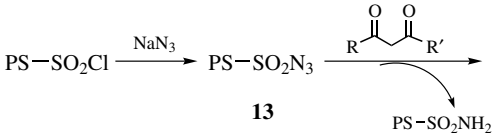
Scavenging of Nucleophiles. PS-TsCl has been shown to scavenge a variety of nucleophiles from solution, including amines, alcohols, oximes, hydrazines, and a Grignard reagent.[13] Stirring the nucleophiles over the resin in 20–50% pyridine in CH_2Cl_2 or dichloroethane at room temperature resulted in >95% scavenging in less than 6 h. The resin-bound nucleophiles were then removed by simple filtration.

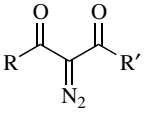
The scavenging function of PS-TsCl was used in combination with the catch-and-release strategy (eq 13) to scavenge phenol **11** while simultaneously transforming a resin-bound aryloxypropanol into aryloxypropylamine (**12**).[14]



Polymer-supported Reagents. Polymer-supported toluenesulfonyl azide **13**[15] was prepared by reaction of a macroreticular *p*-toluenesulfonyl chloride resin (prepared, in turn, by chlorosulfonation of Amberlite XE 305) with excess sodium azide. Resin **13**, a solid-phase equivalent of *p*-toluenesulfonyl azide, can be used for diazo transfer to β-dicarbonyl compounds (eq 14). Unlike tosyl azide, resin **13** does not detonate on shock treatment and is stable at room temperature. Recently, an analogous benzenesulfonyl azide resin has been prepared from PS-TsCl.[16]

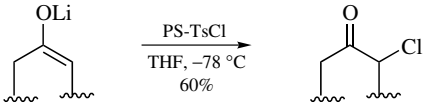
PS-TsCl has also been used as a reagent for α-chlorination of ketones (eq 15).[17] *p*-toluenesulfonyl chloride has been used for the same transformation;[17] however, the solid-supported toluenesulfonyl chloride offers the advantage of rendering the lithium sulfinate by-product insoluble and thus easily removed from the reaction mixture.





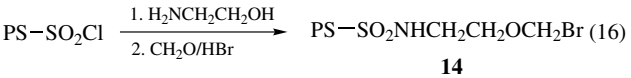
(14)

68-97%



(15)

Bromomethyl methyl ether resin (**14**)[18] was prepared from PS-SO_2Cl by treatment with ethanolamine followed by formaldehyde-HBr (eq 16). Resin **14** was used to bromomethylate aromatic substrates (eq 17),[18] thus providing an alternative to highly carcinogenic halomethylating reagents such as chloromethyl methyl ether.



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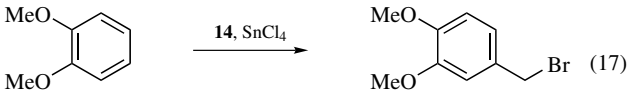
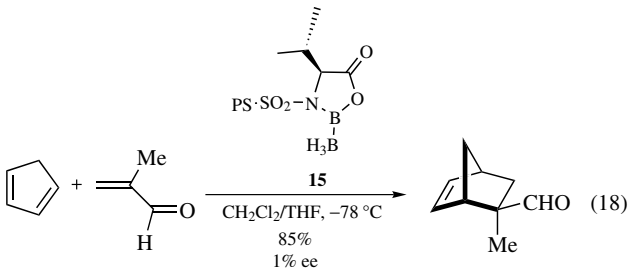


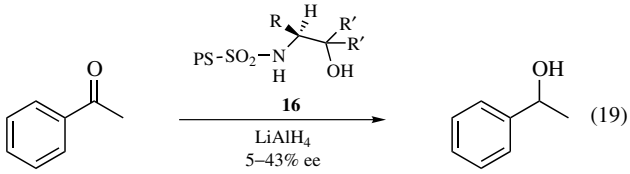
(17)

N-sulfonylamino acid resin (**15**)[1] was prepared from PS-SO_2Cl as a chiral catalyst for the asymmetric Diels–Alder reaction of cyclopentadiene with methacrolein (eq 18). Although resin **15** prepared from PS-SO_2Cl showed very low enantioselectivity (1% ee), similar resins prepared from preformed chiral monomers showed much improved selectivity (57–65% ee).[1]



(18)

Similarly, *N*-sulfonylamino alcohol resins (**16**)[19] have been used as chiral auxiliaries for the asymmetric reduction of ketones by lithium aluminum hydride. Modest enantioselectivities were achieved (5–43% ee) with resins **16** in the reduction of acetophenone (eq 19).[19]



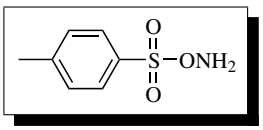
(19)

Related Reagents. Polymer-supported Methanesulfonyl Chloride; Toluenesulfonyl Chloride; Methanesulfonyl Chloride.

1. Kamahori, K.; Tada, S.; Ito, K.; Itsuno, S., *Tetrahedron: Asymmetry* **1995**, *6*, 2547.
2. Huang, W.; He, B., *Chin. J. Reactive Polymers (Engl.)* **1992**, *61*, 1.
3. Hunt, J. A.; Roush, W. R., *J. Am. Chem. Soc.* **1996**, *118*, 9998.
4. Takahashi, T.; Tomida, S.; Inoue, H.; Doi, T., *Synlett* **1998**, 1261.
5. Zhong, H. M.; Greco, M. N.; Maryanoff, B. E., *J. Org. Chem.* **1997**, *62*, 9326.
6. Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B., *Tetrahedron Lett.* **1998**, *39*, 979.
7. Jin, S.; Holub, D. P.; Wustrow, D. J., *Tetrahedron Lett.* **1998**, *39*, 3651.
8. Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E., *Org. Lett.* **2000**, *2*, 89.
9. Hijikuro, I.; Doi, T.; Takahashi, T., *J. Am. Chem. Soc.* **2001**, *123*, 3716.
10. Rueter, J. K.; Nortey, S. O.; Baxter, E. W.; Leo, G. C.; Reitz, A. B., *Tetrahedron Lett.* **1998**, *39*, 975.
11. Pirrung, M. C.; Tumey, L. N., *J. Comb. Chem.* **2000**, *2*, 675.
12. Takahashi, T.; Ebata, S.; Doi, T., *Tetrahedron Lett.* **1998**, *39*, 1369.
13. Hu, F.; Porco, J. A., Jr, *Synth. Purification Lett.* **1998**; 1 (see http://www.argotech.com/sciresources.htm# 2001).
14. Hansen, H. C.; Olsson, R.; Croston, G.; Andersson, C.-M., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2435.
15. Roush, W. R.; Feitler, D.; Rebek, J., *Tetrahedron Lett.* **1974**, *15*, 1391.
16. Green, G. M.; Peet, N. P.; Metz, W. A., *J. Org. Chem.* **2001**, *66*, 2509.
17. Brummond, K. M.; Gesenberg, K. D., *Tetrahedron Lett.* **1999**, *40*, 2231.
18. Warshawsky, A.; Shoef, N., *J. Polym. Sci.: Polym. Chem. Ed.* **1985**, *23*, 1843.
19. Altava, B.; Burguete, I.; Collado, M.; Garcia-Verdugo, E.; Luis, S. V.; Salvador, R. V.; Vicent, M. J., *Tetrahedron Lett.* **2001**, *42*, 1673.

Julianne A. Hunt
Merck & Co. Inc., Rahway, NJ, USA

O-p-Toluenesulfonylhydroxylamine



[52913-14-1] $C_7H_9NO_3S$ (MW 187.22)

InChI = 1/C7H9NO3S/c1-6-2-4-7(5-3-6)12(9,10)11-8/h2-5H, 8H2,1H3

InChIKey = OAIJQSLFIIMPOI-UHFFFAOYAR

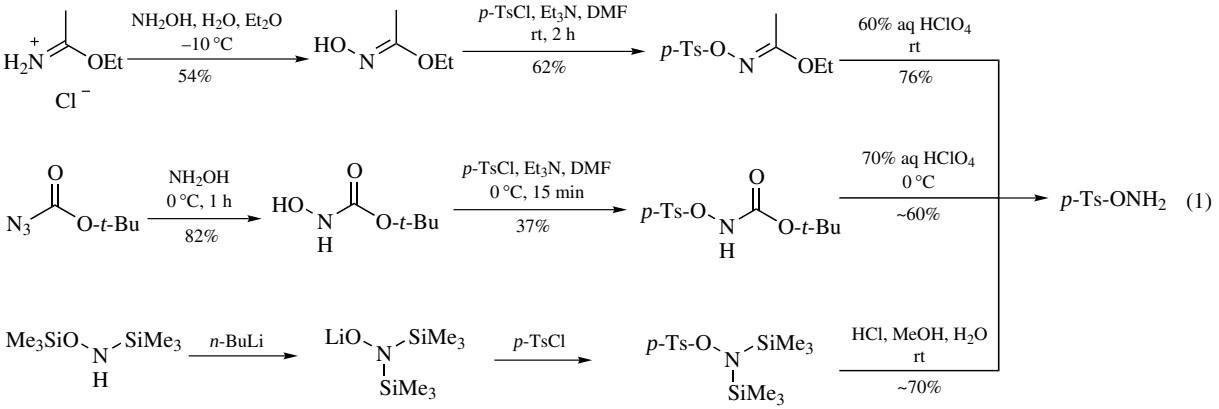
(powerful aminating reagent which is used for aminating five- and six-membered heterocycles; source of nucleophilic nitrogen; used in aziridination reactions)

Alternate Name: tosyloxyamine, TSH.

Physical Data: mp 40 °C (dec.); IR (nujol): 1353, 1176 cm^{-1}.[1]

Solubility: soluble in DCM; insoluble in H_2O.

Form Supplied in: colorless crystals; very unstable in the pure state. The compound should be immediately dissolved in DCM and used in such solutions. Solutions in DCM can be kept for about 1 week.



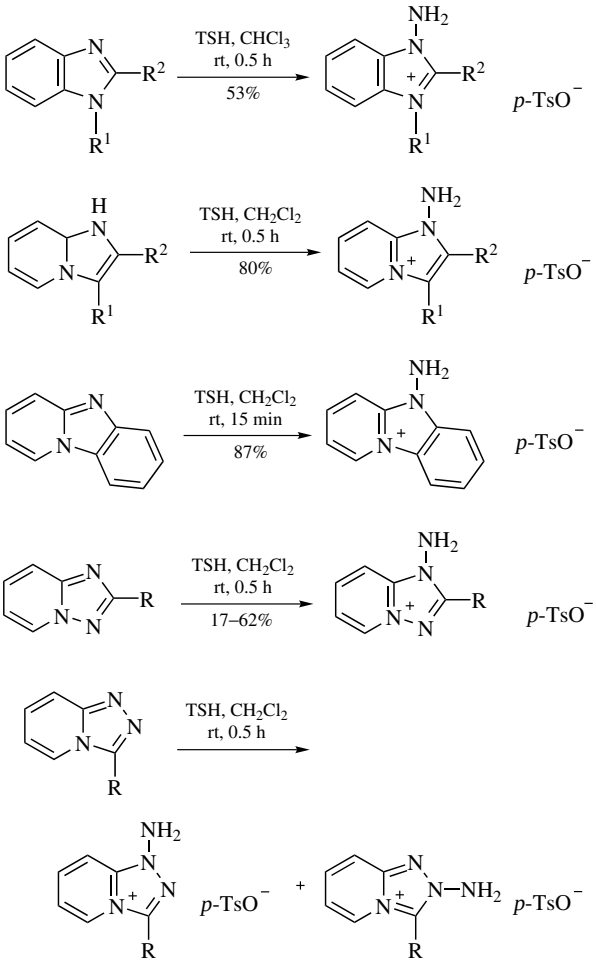
Preparative Methods: TSH can be generated from ethyl acetohydroximate,[3] *t*-butyl *N*-hydroxycarbamate,[1] or *N*,*N*-bis(trimethylsilyl)hydroxylamine by tosylation.[4] All the three procedures are completed by hydrolysis with aqueous $HClO_4$ or HF (eq 1). The first method seems to be the most convenient. Ethyl iminoacetate hydrochloride[5] was treated with hydroxylamine to give ethyl acetohydroximate,[6] which was then tosylated to give *O*-*p*-toluenesulfonylacetohydroximate.[3] The latter compound was finally treated with 60% aq $HClO_4$ at 25 °C. Aqueous work-up and extraction with DCM afforded TSH.[3,7] All steps proceeded in good yields.

Purity: is capricious and not necessary. Dioxane solution is poured very slowly into water under vigorous mechanical stirring to obtain the material as large crystals which can be filtrated quickly before decomposition takes place. The contents of TSH in solution can be established by iodometric titration.[2] TSH can be characterized by its acetone oxime[1] or its *N*-acylated derivatives.[2]

Handling, Storage, and Precaution: the neat compound is very unstable and deflagrates sometimes in minutes to a black tar. Used in DCM solution. Such solutions can be kept for about 1 week. No toxicity data are available. The compound should be used only in a well-ventilated fume hood. The neat compound should be handled with great care due to its instability.

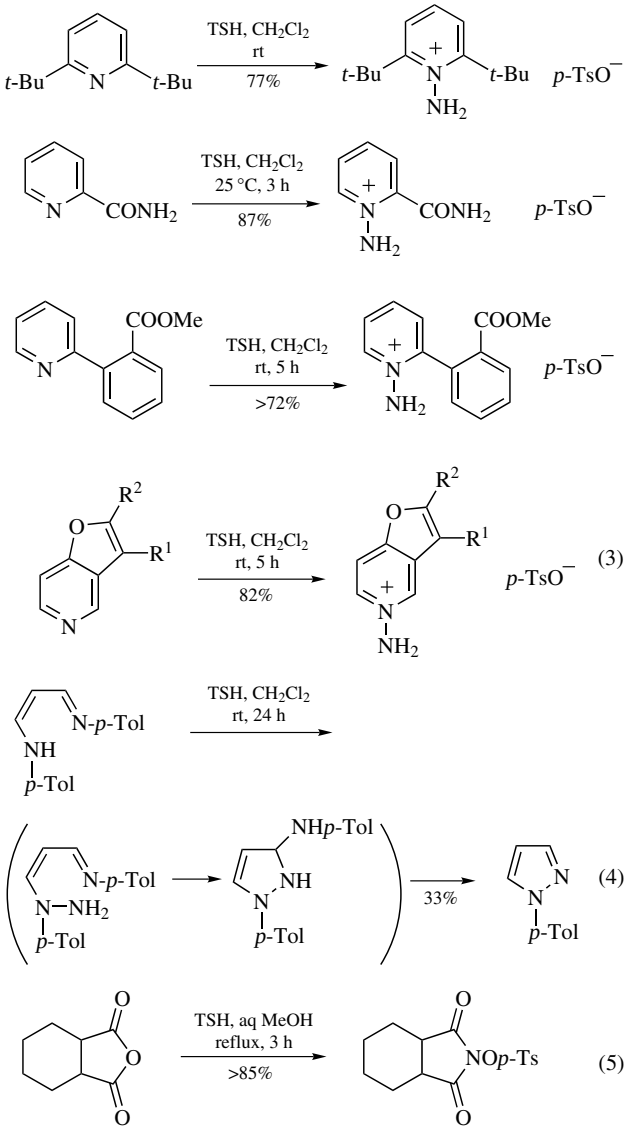
***N*-Amination.** TSH is a source of electrophilic NH_2 and a powerful aminating agent. It is more reactive and less costly to prepare than the much more stable *O*-mesitylsulfonylhydroxylamine (MSH), which has an extensive record of usage.[2,3] TSH has been used to *N*-aminate nitrogen atoms in five- and six-membered heterocycles. Thus TSH *N*-aminated 1-substituted benzimidazoles at *N*-3 to give 1-amino-3-substituted benzimidazolium salts.[3] Similarly, TSH was more efficient than hydroxylamine-*O*-sulfonic acid in *N*-amination of imidazo[1,2-*a*]pyridines, 1,2,4-triazolo[1,5-*a*]pyridines, and 1,2,4-triazolo[4,3-*a*]pyridines.[3] The latter compound produced a mixture of two isomers, similar to methylation (eq 2).

TSH readily *N*-aminates sterically hindered pyridines such as 2,6-di-*tert*-butylpyridine, which can only be *N*-alkylated under forcing conditions.[7] Ethyl pyridine-2-carboxylate,[8] 2-carbamidopyridines,[8], methyl 2-(2-pyridyl)benzoate,[9] and furo[3,2-*c*]-pyridines[10] were likewise *N*-aminated in high yields under mild conditions (eq 3).

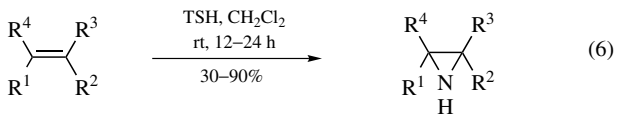


N-aminopyridines are excellent precursors for further cyclization reactions.[8,9] Treatment of 1-*p*-(tolylamino)-3-(*p*-tolylimino)-1-propene with TSH afforded 1-*p*-tolylpyrazole in modest yield (eq 4). Most likely TSH *N*-aminates the enamine nitrogen to give an enhydrazine, which subsequently adds to the imine carbon. Finally, *p*-toluidine is eliminated resulting in aromatization. Under similar conditions, neither silyloxy-, alkyloxy-, nor benzoyloxy amines gave *N*-amination.[11]

***C*-Amination.** TSH may also serve as a source of nucleophilic nitrogen. Thus, tetrahydrophthalic anhydride reacted with TSH to give 2-(*p*-tolyloxy)-hexahydro-isoindole-1,3-dione (eq 5).[12]



Aziridination. TSH aminates alkenes in a stereospecific fashion to give aziridines in moderate to high yields (eq 6).[13] The reaction took place in DCM solution for 12–24 h at room temperature. (*Z*)- and (*E*)-1,2 dialkyl substituted alkenes were aziridinated smoothly while stilbene failed to react with TSH. No details on aziridination of tri- and tetrasubstituted alkenes were given.

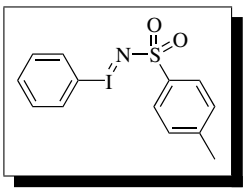


Related Reagents. *O*-Mesitylsulfonylhydroxylamine; Hydroxylamine *O*-Sulfonic Acid; *O*-Trimethylsilylhydroxylamine; *O*-Benzoyl Hydroxylamine.

1. Carpino, L. A., *J. Am. Chem. Soc.* **1960**, *82*, 3133.
2. Tamura, Y.; Minanikawa, J.; Ikeda, M., *Synthesis* **1977**, 1.
3. Glover, E. E.; Rowbottom, K. T., *J. Chem. Soc., Perkin Trans. 1* **1976**, 367.
4. King, F. D.; Walton, D. R. M., *Synthesis* **1975**, *12*, 788.
5. Dox, A. W., *Org. Synth. Coll. Vol.* **1932**, *1*, 5.
6. Millen, M. H.; Waters, W. A., *J. Chem. Soc. (B)* **1968**, 408.
7. Gawinecki, R.; Kanner, B., *Monatsh. Chem.* **1994**, *125*, 35.
8. Batori, S.; Messmer, A., *J. Heterocycl. Chem.* **1988**, *25*, 437.
9. Timari, G.; Hajos, G.; Batori, S.; Messmer, A., *Chem. Ber.* **1992**, *125*, 929.
10. Benckova, M.; Krutosikova, A., *Collect. Czech. Chem. Commun.* **1999**, *64*, 539 .
11. Alcazar, J.; Almena, I.; Begtrup, M.; de la Hoz, A., *J. Chem. Soc., Perkin Trans. 1* **1995**, 2773.
12. Ishikawa, M.; Fujimoto, M.; Sakai, M.; Matsumoto, A., *Chem. Pharm. Bull.* **1968**, *16*, 622.
13. Bottaro, J., *J. Chem. Soc., Chem. Commun.* **1980**, 560.

Mikael Begtrup
Danish University of Pharmaceutical Sciences, Copenhagen, Denmark

[*N*-(*p*-Toluenesulfonyl)imino]-phenyliodinane



[55962-05-5] $C_{13}H_{12}INO_2S$ (MW 373.23)
InChI = 1/C13H12INO2S/c1-11-7-9-13(10-8-11)18(16,17)15-14-12-5-3-2-4-6-12/h2-10H,1H3
InChIKey = WECCHUKCGHQAQJ-UHFFFAOYAQ

(nitrogen atom source; reacts with heteroatom lone pairs to form ylides; capable of C–H bond insertion or alkene aziridination in the presence of transition metal catalysts)

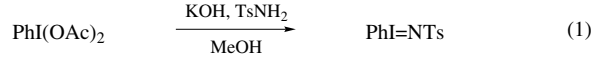
Physical Data: mp 102–104 °C (dec).[1]

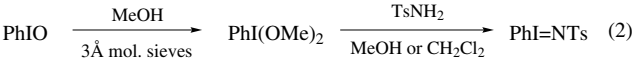
Solubility: v sl sol nonpolar solvents; sol DMSO (decomposes slowly); reacts with THF, MeOH.

Form Supplied in: light yellow solid, commercially available.

Analysis of Reagent Purity: ^{1}H NMR spectra can be obtained in DMSO-d_6, although the reagent slowly reacts with the solvent. Other assays include iodometric analysis[1] and reaction with triphenylphosphine to form the phosphinimine.[2]

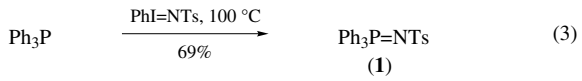
Preparative Methods: prepared by the reaction of $PhI(OAc)_2$ with $TsNH_2$ and KOH in MeOH, from which the product precipitates upon addition of water (eq 1).[1] Another preparation employs the reaction of $TsNH_2$ with $PhI(OMe)_2$ in MeOH or in CH_2Cl_2 (eq 2).[2]



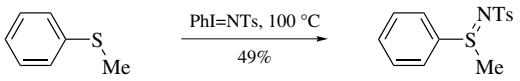


Handling, Storage, and Precautions: store at −20 °C; should be used within 6 months. The reagent can be weighed out in air. No known toxicity. Use in a fume hood.

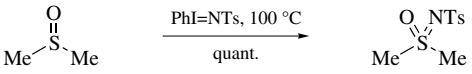
Nitrogen Atom Transfer to Heteroatoms. PhI=NTs reacts with heteroatom lone pairs to generate ylides.[1] Reaction with triphenylphosphine at 100 °C affords 69% of the phosphinimine (**1**) (eq 3). Likewise, PhI=NTs reacts with thioanisole to generate the iminosulfurane (**2**) in 49% yield (eq 4) and with dimethyl sulfoxide to quantitatively produce the sulfoximine (**3**) (eq 5).



(3)

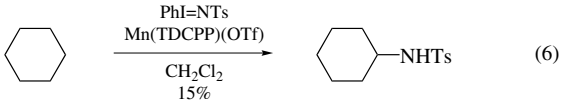


(4)



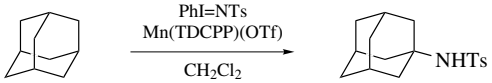
(5)

Amination of Alkanes and Alkenes. PhI=NTs can be employed as a nitrogen source in the transition metal-catalyzed amination of alkanes and the allylic amination of alkenes. Manganese porphyrin complexes catalyze the amination of cyclohexane to generate *N*-tosylcyclohexylamine in 15% yield, while adamantane is aminated in 56% yield (eqs 6 and 7).[3] Manganese porphyrins also catalyze the amination of alkenes to generate allylic amine derivatives.[4] In this manner, *N*-tosyl-2-cyclohexeneamine was synthesized in 70% yield based on oxidant (eq 8). The amination of open-chain alkenes is hampered by attenuated reactivity and poor regioselectivity.

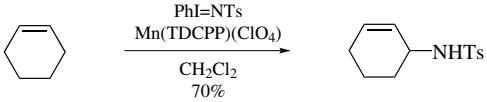


(6)

TDCPP = tetrakis(2,6-dichlorophenyl)porphyrin

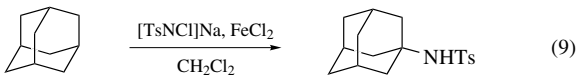


(7)



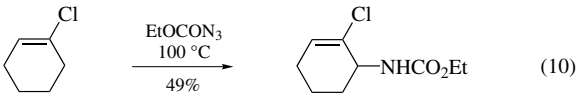
(8)

A complex generated in situ by the addition of iron(II) chloride to chloramine-*T* effects similar aminations of hydrocarbons.[5] When adamantane is introduced to a solution of this complex, *N*-tosyladamantan-1-amine is isolated in 63% yield (eq 9). Extension of the reaction to other substrates is complicated by the generation of chlorine-containing products.



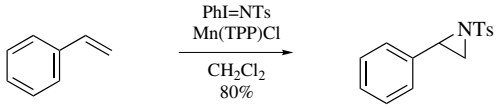
(9)

The insertion of nitrenes, generated via the photolysis or thermolysis of azides, into C–H bonds is well known, although the yields are generally poor.[6,7] However, when ethyl azidoformate is thermolyzed in the presence of 1-chlorocyclohexene, the allylic insertion product is formed in 49% yield (eq 10).[8] In this case it is not clear if the product is formed through direct insertion or by the ring opening of an aziridine intermediate.



(10)

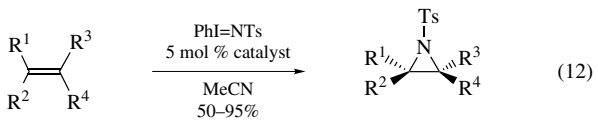
Aziridination of Alkenes. Iron– and manganese–porphyrin complexes catalyze the reaction of PhI=NTs with alkenes to form the corresponding *N*-tosylaziridines.[9] Mn(TPP)Cl is generally a better catalyst than the analogous iron complex, affording 80% of the aziridine from the reaction with styrene (eq 11). Good yields are also obtained in the manganese-catalyzed reactions with 1,1- and 1,2-diphenylethylenes.[10] Yields of aziridines derived from aliphatic alkenes remain low and are complicated by the formation of allylic amines.



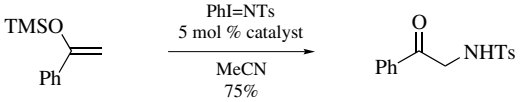
(11)

TPP = tetraphenylporphyrin

Copper-based complexes have been found to be excellent catalysts for the aziridination of alkenes employing PhI=NTs as the nitrene precursor (eq 12).[11] Both Cu^{I} and Cu^{II} efficiently catalyze the reaction, and the best results are usually obtained with the cationic complexes tetrakis(acetonitrile)copper(I) perchlorate and copper(II) trifluoromethanesulfonate Good yields are obtained with a variety of substrates, including aliphatic alkenes and enolsilanes (eq 13), the latter delivering α-amino ketones upon hydrolysis of the intervening silyloxyaziridine.



(12)

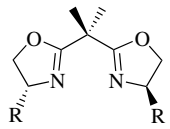


(13)

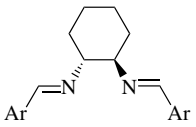
Other nitrene precursors have been employed in the aziridination of alkenes. Azides have been shown to form aziridines when photolyzed or thermolyzed in the presence of alkenes, though

these reactions usually exhibit low yields.[12,13] However, the possibility of a transition metal-catalyzed process remains. In 1968, it was reported that heating benzenesulfonyl azide with cyclohexene in the presence of copper powder produces the corresponding aziridine, albeit in low yield (15%).[14] Pd^0 catalyzes the aziridination of allylic ethers with methyl azidoformate.[15]

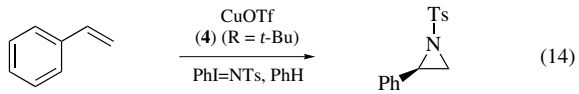
Asymmetric Aziridination of Alkenes. The copper-catalyzed aziridination reaction can be rendered enantioselective by the addition of chiral ligands. The first example of an enantioselective aziridination of an alkene employed the bis(oxazoline) ligand (**4**) (R = *t*-Bu) and copper(I) trifluoromethanesulfonate as the metal catalyst (eq 14).[16] This catalyst system affords the aziridine in 97% yield and 61% ee. Other reports have appeared subsequently regarding the extended scope of this reaction.[17–21] Important contributions to this area include the copper/bis-(oxazoline)-catalyzed aziridination of aryl acrylate esters (eq 15)[20] and the copper/bis(imine)-catalyzed aziridination of cyclic *cis*-alkenes with the bis(imine) ligand (**5**) (eqs 16 and 17).[19]



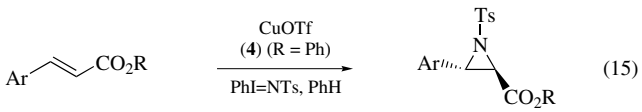
(**4**) R = Ph, *t*-Bu



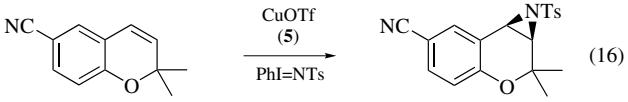
(**5**) Ar = 2,6-$Cl_2C_6H_3$



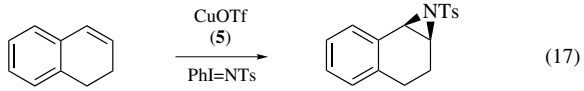
61% ee (14)



94–96% ee (15)

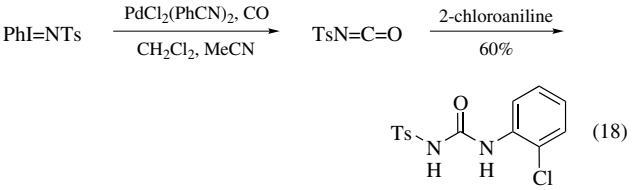


>98% ee (16)



87% ee (17)

Formation of Isocyanates. The Pd-catalyzed reaction of PhI=NSO_2Ar in the presence of CO generates the isocyanates $ArSO_2NCO$.[22] Thus bis(benzonitrile)dichloropalladium(II) catalyzes the formation of the isocyanate TsNCO (which can be isolated as the urea **6** in 60% yield after reaction with 2-chloroaniline) with PhI=NTs (eq 18). This reaction has been reported for several arylsulfonylimino iodinanes. Similar results can be achieved, however, by employing the less expensive chloramine-T and its derivatives as reagents.[23]



(**6**) (18)

1. Yamada, Y.; Yamamoto, T.; Okawara, M., *Chem. Lett.* **1975**, *4*, 361.
2. Besenyei, G.; Németh, S.; Simándi, L. I., *Tetrahedron Lett.* **1993**, *34*, 6105.
3. Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D., *Nouv. J. Chim.* **1989**, *13*, 651.
4. Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D., *Tetrahedron Lett.* **1988**, *29*, 1927.
5. Barton, D. H. R.; Hay-Motherwell, R. S.; Motherwell, W. B., *J. Chem. Soc., Perkin Trans. 1* **1983**, 445.
6. *Azides and Nitrenes–Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: New York, 1984; 542.
7. Meth-Cohn, O., *Acc. Chem. Res.* **1987**, *20*, 18.
8. Pellacani, L.; Persia, F.; Tardella, P. A., *Tetrahedron Lett.* **1980**, *21*, 4967.
9. Mansuy, D.; Mahy, J. P.; Dureault, A.; Bedi, G.; Battioni, P., *J. Chem. Soc., Chem. Commun.* **1984**, 1161.
10. Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D., *J. Chem. Soc., Perkin Trans. 2* **1988**, *2*, 1517.
11. Evans, D. A.; Faul, M. M.; Bilodeau, M. T., *J. Org. Chem.* **1991**, *56*, 6744.
12. Deyrup, J. A. In *Chemistry of Heterocyclic Compounds*; Hassner, A., Ed.; Wiley: New York, 1983; Vol. 42, p 1.
13. Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, p 47.
14. Kwart, H.; Khan, A. A., *J. Am. Chem. Soc.* **1967**, *89*, 1951.
15. Migita, T.; Chiba, M.; Takahashi, K.; Saitoh, N.; Nakaido, S.; Kosugi, M., *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3943.
16. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M., *J. Am. Chem. Soc.* **1991**, *113*, 726.
17. Lowenthal, R. E.; Masamune, S., *Tetrahedron Lett.* **1991**, *32*, 7373.
18. O'Connor, K. J.; Wey, S. J.; Burrows, C. J., *Tetrahedron Lett.* **1992**, *33*, 1001.
19. Li, Z.; Conser, K. R.; Jacobsen, E. N., *J. Am. Chem. Soc.* **1993**, *115*, 5326.
20. Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M., *J. Am. Chem. Soc.* **1993**, *115*, 5328.
21. Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T., *Synlett* **1993**, 469.
22. Besenyei, G.; Simándi, L. I., *Tetrahedron Lett.* **1993**, *34*, 2839.
23. Besenyei, G.; Németh, S.; Simándi, L. I., *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1147.

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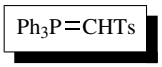
p-Toluenesulfonylmethylene Triphenylphosphorane



[5554-81-4] $C_{26}H_{23}O_2PS$ (MW 430.50)

InChI = 1/C26H23O2PS/c1-22-17-19-26(20-18-22)30(27,28)21-29(23-11-5-2-6-12-23,24-13-7-3-8-14-24)25-15-9-4-10-16-25/h2-21H,1H3

InChIKey = UDJLRPGUUHGFBI-UHFFFAOYAN

(sulfonyl-stabilized phosphorane reagent used for Wittig alkenation reactions to give (*E*)-vinyl sulfones on reactions with aldehydes;[1,2] synthesis of (*Z*)-γ-keto-α,β-unsaturated sulfones with chromium alkoxycarbene complexes[3])

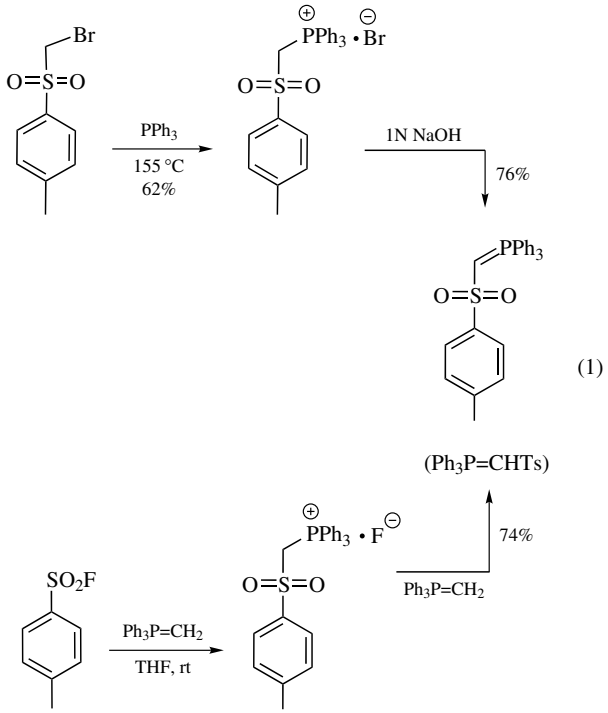
Alternate Names: tosylmethylenetriphenylphosphorane.

Physical Data: mp 186–187 °C,[4] IR,[4] UV,[4] ^{1}H NMR.[5]

Solubility: sol $CHCl_3$ (15 mg 1.0 mL^{-1}); fairly sol benzene, THF, EtOH (5 mg, 1.0 mL^{-1}); insol water.

Form Supplied in: white crystalline powder.

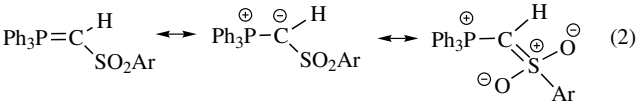
Preparative Methods: generated by deprotonation of the triphenyl(*p*-toluenesulfonyl)methylphosphonium halide salts, which can be prepared by heating of bromomethyl *p*-tolyl sulfone and triphenylphosphine[4,5] or by treatment of *p*-toluenesulfonyl fluoride with methylenetriphenylphosphorane[5] (eq 1).



(1)

Handling, Storage, and Precautions: there is no special handling required but storage at 5 °C in a sealed container and drying prior to use are recommended.

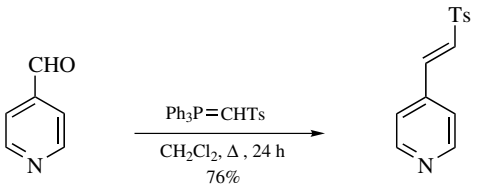
Weakly Basic Phosphorus Ylide. Deprotonation of the phosphonium halides produces a phosphorane in which the negative charge on the α-carbon is stabilized primarily by sulfur and phosphorus *d* orbitals (eq 2; Ar = 4-$CH_3C_6H_4$).[4] The single crystal X-ray structure revealed that the central carbon is sp^2 hybridized and that the mean length of the P–C_6H_5 bonds is 1.81 Å and the length between phosphorus and α-carbon atoms is 1.71 Å, which is rather longer than expected from interpolation of the corresponding single- and triple-bond lengths.[6] The sulfone sulfur is tetrahedral and the tolyl ring is perpendicular to the α-carbon–sulfur–aromatic carbon plane producing considerable steric factors that result in decreased reactivity.[4]



(2)

Wittig Alkenation Reactions. The tosylmethylene phosphorane is classified as a stabilized Wittig reagent[7] because of the extra negative charge stabilization by the sulfone substituent on the ylidic carbon. Other stabilized ylides include (methoxy- or ethoxycarbonylmethylene)triphenylphosphorane, cyanomethylenetriphenylphosphorane, and formyl- or acetylmethylenetriphenylphosphorane. These ylides are normally less reactive towards aldehydes and ketones than the nonstabilized alkylidenephosphoranes but they usually favor the production of *E*-alkenes with higher stereoselectivity.[7] Decreased reactivity of the sulfonyl-stabilized phosphorane, as compared to the carbonyl-stabilized reagents, is related rather to steric factors, because the sulfone group is worst than the carbonyl group at stabilizing an adjacent carboanion.[4] If more reactive reagents are required for preparation of the synthetically versatile vinyl sulfones,[8,9] diethyl methylsulfonylmethylphosphonate or diethyl phenylsulfonylmethylphosphonate[10] can be employed in the Horner–Wadsworth–Emmons (HWE) procedure[7] or phenylsulfonyl(trimethylsilyl)methane in the Peterson olefination.[11] The by-products formed during HWE (water soluble phosphates) and Peterson alkenylations are easier to remove than the triphenylphosphine oxide produced during reactions utilizing triphenylphosphorane reagents.

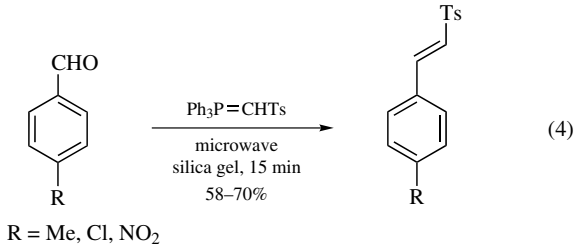
Reactions with Aldehydes. The sulfonyl-stabilized phosphorane reagent has been used for Wittig alkenation of aldehydes.[4,12] For example, condensation with isonicotinaldehyde gave the α,β-unsaturated sulfone as a single *E* isomer in 76% yield[12] (eq 3). It is noteworthy that analogous reaction with (methylsulfonylmethylene)triphenylphosphorane[5] produced the corresponding methylsulfonyl alkene as a 1:1 mixture of the *E/Z* isomers.[12]



(3)

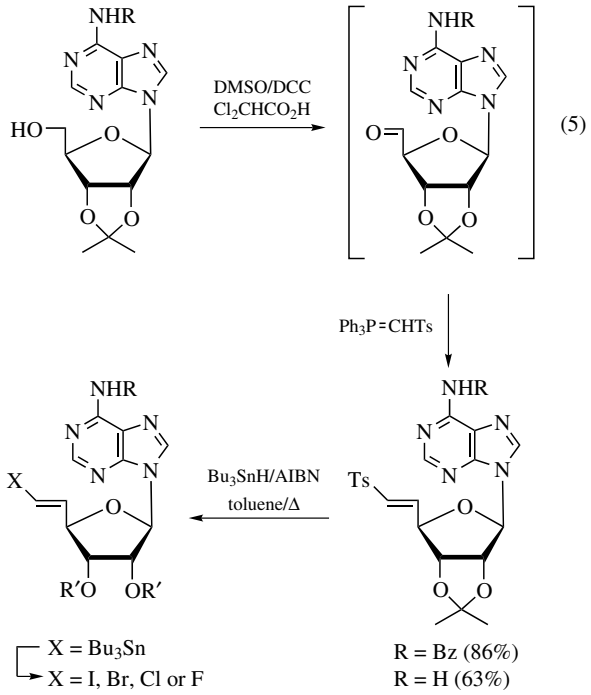
The rate of the Wittig alkenation was dramatically improved when reactions were carried out under irradiation in a domestic microwave oven using silica gel as an effective support to give *E* only products in 15 min (eq 4).[2] Thus, condensation of *p*-nitrobenzaldehyde gave the vinyl sulfone (R = NO_2) in 58%

yield after only 15 min under microwave conditions, while standard condensation in chloroform required 3 days at rt to give the same product in 53% yield.[4] The microwave method was also adapted to aliphatic aldehydes.[2]



(4)

Olefination of the Nucleoside-5′-aldehydes. Moffatt oxidation of 2′, 3′-*O*-isopropylideneadenosine yields the 5′-aldehyde, which when treated *in situ* with tosylmethylene phosphorane gave the chain-extended (*E*)-vinyl sulfone in high yields under the "base-free" conditions (eq 5).[1] It is noteworthy that direct introductions of an alkylidene group (particularly the methylene group) at C5′ of the nucleosides has met with limited success, presumably owing to the instability of the 5′-aldehydes under the experimental conditions, which usually required employing strong bases for the generation of the nonstabilized alkylidenephosphoranes or α-phosphoryl or α-silyl carbanions.[1] The low basicity of the tosylmethylene phosphorane allows for mild alkenylation without affecting the base-sensitive protection groups (e.g., benzoyl[1] or acetyl[13]) or causing epimerization at C4′ of nucleoside 5′-aldehydes.[1,13,16] Furthermore, reactions of the nucleoside 5′-aldehydes with Ph_3P=CHTs occurred with *E* stereoselectivity,[1,13,16] while condensations of the ribose-derived 5′-aldehydes with (ethoxycarbonylmethylene)triphenylphosphorane gave the corresponding acrylates as *E*/*Z* mixtures (86:14 to 8:92) depending on the solvent used.[17]

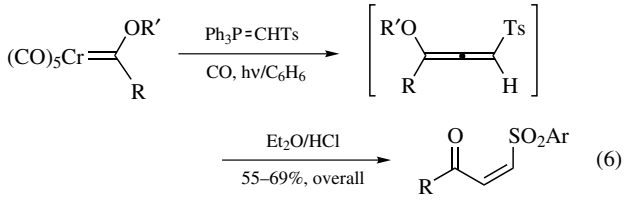


(5)

Isomerization of the vinyl tosyl group to a 4′,5′-unsaturated allylic tosyl derivative occurred with classical reductive sulfone cleavage methods and in solutions of aqueous (NaOH) or organic (**DBU**) bases.[1,14] However, radical stannyldesulfonylation of the vinyl 6′-(*E*)-sulfone with tributylstannane yielded separable mixture (*E*/*Z*, ~4.2:1) of the vinyl 6′-stannanes (X = Bu_3Sn).[18] Quantitative halodestannylation with **NBS** or **NIS** and deprotections gave the Wittig-type 5′-deoxy-5′-(halomethylene)adenosines (X = I or Br, R = R′ = H), which were found to be potent mechanism-based inhibitors of *S*-adenosyl-L-homocysteine hydrolase with antiviral and anticancer activity.[18] Protiodestannylation with ammonium fluoride in ethanol at reflux produced 5′-deoxy-5′-methyleneadenosine (X = H).[18]

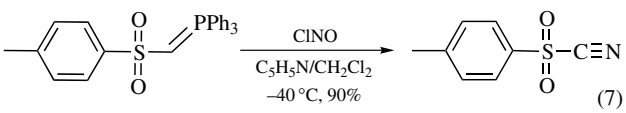
The above sequence has a general character and was applied for the synthesis of various 6′-substituted-5′,6′-unsaturated hexofuranosyl nucleosides derived from uridine,[14,19] L-adenosine,[15] 3′-deoxyadenosine,[13] and 6-*N*-cyclopropyladenosine.[16] The vinyl stannanes and halides were used as convenient precursors for further modifications. Thus, Stille coupling of vinyl 6′-stannanes with ethyl iodopropenoates gave sugar-modified diene analogs of nucleosides[20] and Sonogashira coupling of iodomethylene precursors with (trimethylsilyl)acetylene produced the corresponding enyne derivatives.[21]

Photochemical Reactions with Alkoxychromium Carbene Complexes. Photolysis of chromium alkoxycarbene complexes in the presence of tosylmethylene phosphorane [or ester stabilized ylides such as (methoxycarbonylmethylene)-triphenylphosphorane] under an atmosphere of carbon monoxide produced allenes. Such reactive allenes (EWG at C1 and electron donating group at C3) hydrolyzed to give γ-keto-α,β-unsaturated sulfones with *Z*-stereoselectivity (eq 6).[3]



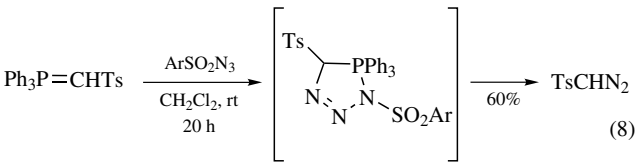
(6)

Formation of Sulfonyl Cyanide. Tosylmethylene phosphorane reacts readily with nitrosyl chloride to provide *p*-toluenesulfonyl cyanide via a Wittig-like fragmentation of the α-nitroso phosphonium intermediate with expulsion of Ph_3PO (eq 7).[22]



(7)

Formation of *(p-Toluenesulfonyl)diazomethane.* 1,3-Dipolar cycloaddition of PhP=CHTs with aryl azides provided tosyldiazomethane via the fragmentation of the phosphatriazole-type intermediary adduct (eq 8).[23]



(8)

1. Wnuk, S. F.; Robins, M. J., *Can. J. Chem.* **1991**, *69*, 334.
2. Fu, C.; Xu, C.; Huang, Z.-Z.; Huang, X., *Org. Prep. Proc. Int.* **1997**, *29*, 587.
3. Sestrick, M. R.; Miller, M.; Hegedus, L. S., *J. Am. Chem. Soc.* **1992**, *114*, 4079.
4. Speziale, A. J.; Ratts, K. W., *J. Am. Chem. Soc.* **1965**, *87*, 5602.
5. van Leusen, A. M.; Reith, B. A.; Iedema, J. W.; Strating, J., *Recl. Trav. Chim. Pays-Bas.* **1972**, *91*, 37.
6. Wheatley, P. J., *J. Chem. Soc.* **1965**, 5785.
7. Maryanoff, B. E.; Reitz, A. B., *Chem. Rev.* **1989**, *89*, 863.
8. Simpkins, N. G., *Tetrahedron* **1990**, *46*, 6951.
9. Meadows, D. C.; Gervay-Hague, J., *Med. Res. Rev.* **2006**, *26*, 793.
10. Blumenkopf, T. A., *Synth. Commun.* **1986**, *16*, 139.
11. Ager, D. J., *Org. React.* **1990**, *38*, 1.
12. Holler, M.; Sin, H. S.; James, A.; Burger, A.; Tritsch, D.; Biellmann, J.-F., *Chem. Eur. J.* **2000**, *6*, 2053.
13. Robins, M. J.; Neschadimenko, V.; Ro, B.- O.; Yuan, C.- S.; Borchardt, R. T.; Wnuk, S. F., *J. Org. Chem.* **1998**, *63*, 1205.
14. Wnuk, S. F.; Dalley, N. K.; Robins, M. J., *Can. J. Chem.* **1991**, *69*, 2104.
15. Wang, J.- F.; Yang, X.- D.; Zhang, L.- R.; Yang, Z.- J.; Zhang, L-H., *Tetrahedron* **2004**, *60*, 8535.
16. Rapp, M.; Haubrich, T. A.; Perrault, J.; Mackey, Z. B.; McKerrow, J. H.; Chiang, P. K.; Wnuk, S. F., *J. Med. Chem.* **2006**, *49*, 2096.
17. Tronchet, J. M. J.; Gentile, B., *Helv. Chim. Acta* **1979**, *62*, 2091.
18. Wnuk, S. F.; Yuan, C.- S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E.; Robins, M. J., *J. Med. Chem.* **1994**, *37*, 3579.
19. Wnuk, S. F.; Robins, M. J., *Can. J. Chem.* **1993**, *71*, 192.
20. Wnuk, S. F.; Ro, B.-O.; Valdez, C. A.; Lewandowska, E.; Valdez, N. X.; Sacasa, P. R.; Zhang, J.; Borchardt, R. T.; De Clercq, E., *J. Med. Chem.* **2002**, *45*, 2651.
21. Wnuk, S. F.; Lewandowska, E.; Sacasa, P. R.; Crai, L. N.; Zhang, J.; Borchardt, R. T.; De Clercq, E., *J. Med. Chem.* **2004**, *47*, 5251.
22. van Leusen, A. M.; Iedema, A. J. W.; Strating, J., *J. Chem. Soc., Chem. Commun.* **1968**, 440.
23. van Leusen, A. M.; Reith, B. A.; van Leusen, D., *Tetrahedron* **1975**, *31*, 597.

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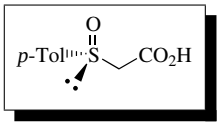
(*R*)-(+)-*p*-Tolylsulfinylacetic Acid



[88981-65-1] $C_9H_{10}O_3S$ (MW 198.26)

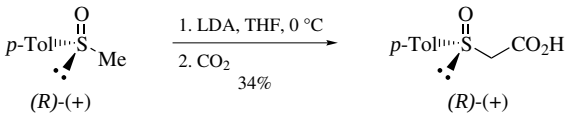
InChI = 1/C9H10O3S/c1-7-2-4-8(5-3-7)13(12)6-9(10)11/h2-5H, 6H2,1H3,(H,10,11)/t13-/m1/s1/f/h10H

InChIKey = VOUUVAHSMCKLTG-SWCQUYOEDR

(optical resolution of amines[1,3,4])

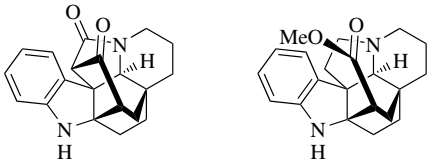
Physical Data: $[\alpha]_D = +143.5°$ (acetone, $c = 33.0$). The absolute configuration of this reagent (and other arylsulfinyl acetic acids) is characterized by two CD Cotton effects which are observed in the presence of the metal cluster $[Mo_2(OAc)_4]$ in DMSO solution above 300 nm.[2]

Preparative Methods: prepared by carboxylation of (*R*)-(+)-methyl *p*-tolyl sulfoxide carbanion generated with lithium diisopropylamide (eq 1).[1]



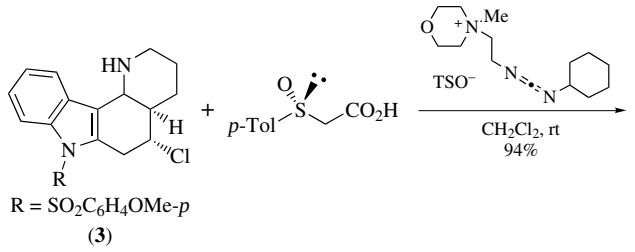
(1)

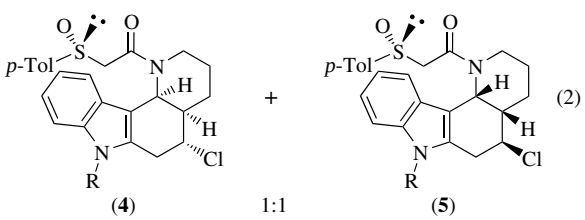
Optical Resolution of Indole Alkaloid Precursors. This reagent has been used for optical resolutions of tetracyclic alkaloids such as 10,22-dioxokopsane (**1**).[1] and kopsinine (**2**).[3]



(**1**) (**2**)

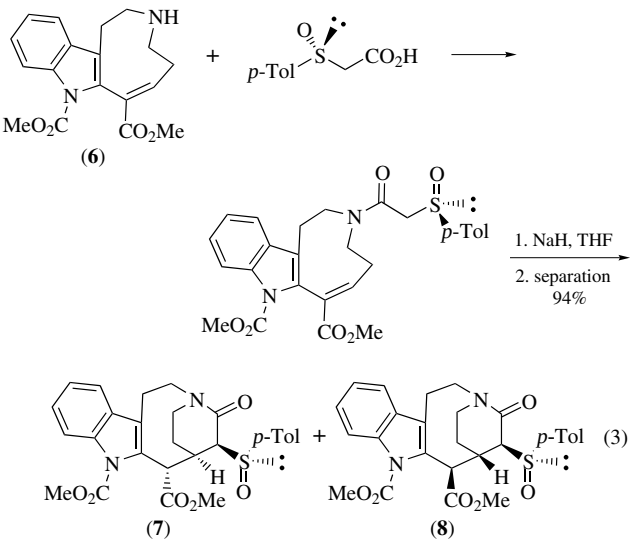
The racemic tetracyclic amine (**3**) can be coupled to (*R*)-(+)-*p*-tolylsulfinylacetic acid using the modified carbodiimide reagent 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate to give the diastereomeric sulfinyl amides (**4**) and (**5**) (eq 2), which are readily separated by HPLC.[1,3]





(2)

Similarly, in a total synthesis of strychnine, the optical resolution was carried out by separation of the sulfinyl lactam diastereomers (**7**) and (**8**), which were obtained from the heptacyclic indole alkaloid precursor (**6**); this was first transformed with (*R*)-(+)-*p*-tolylsulfinylacetic acid into the corresponding sulfinyl amide and then converted to the diastereomeric lactams (**7**) and (**8**) by an intramolecular conjugate addition (eq 3).[4]



1. Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C., *J. Am. Chem. Soc.* **1984**, *106*, 2105.
2. Drabowicz, J.; Mikolajczyk, M., *Croat. Chem. Acta* **1989**, *62*, 423.
3. Magnus, P.; Brown, P., *J. Chem. Soc., Chem. Commun.* **1985**, 184.
4. Magnus, P.; Melvyn, G.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N., *J. Am. Chem. Soc.* **1992**, *114*, 4403.

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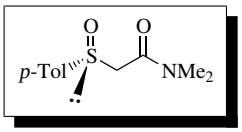
(*R*)-(+)-α-(*p*-Tolylsulfinyl)-*N*,*N*-dimethylacetamide

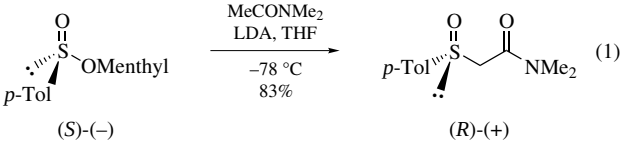


[72298-22-7] $C_{11}H_{15}NO_2S$ (MW 225.34)
InChI = 1/C11H15NO2S/c1-9-4-6-10(7-5-9)15(14)8-11(13)12(2)3/h4-7H,8H2,1-3H3/t15-/m1/s1
InChIKey = MBBXNPFJTLOVFQ-OAHLLOKOBG

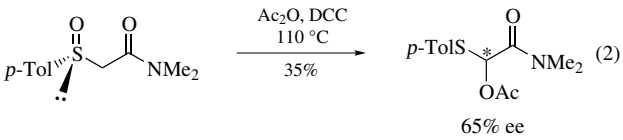
(asymmetric aldol-type condensation[1,2])

Physical Data: $[\alpha]_D = +194.7°$ ($CHCl_3$, $c = 1$).

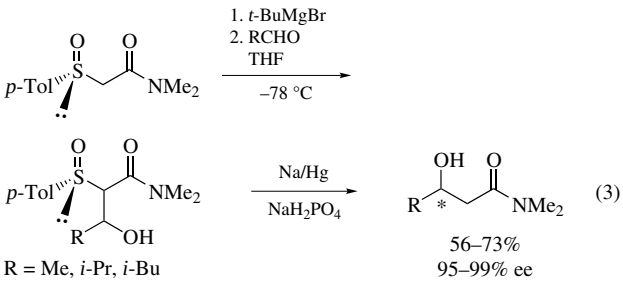
Preparative Method: prepared[1,2] by reaction of lithio-*N*,*N*-dimethylacetamide with (*S*)-(−)-menthyl *p*-toluenesulfinate (eq 1).



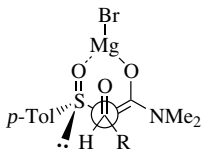
The Pummerer reaction of optically active (*R*)-(+)-α-(*p*-tolylsulfinyl)-*N*,*N*-dimethylacetamide with acetic anhydride in the presence of 1,3-dicyclohexylcarbodiimide is highly stereoselective, affording the corresponding α-acetoxy sulfide in moderate yield but with nearly 70% ee (eq 2).[3,4] The recovered starting sulfoxide is obtained in 63% yield.



Good asymmetric induction is also observed during the aldol-type condensation of the magnesium enolate of (*R*)-(+)-α-(*p*-tolylsulfinyl)-*N*,*N*-dimethylacetamide with aldehydes (eq 3).[1,2]



A model (**1**), similar to that proposed for aldol-type condensation of α-sulfinyl esters,[5] has been proposed to predict the chirality of the resulting β-hydroxy amides.



1. Annunziata, R.; Cinquini, M.; Cozzi, F.; Montanari, F.; Restelli, A., *J. Chem. Soc., Chem. Commun.* **1983**, 1138.
2. Annunziata, R.; Cinquini, M.; Cozzi, F.; Montanari, F.; Restelli, A., *Tetrahedron* **1984**, *40*, 3815.
3. Numata, T.; Itoh, O.; Oae, S., *Tetrahedron Lett.* **1979**, *21*, 1869.
4. Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S., *Bull. Chem. Soc. Jpn.* **1983**, *56*, 257.
5. Mioskowski, C.; Solladié, G., *Tetrahedron* **1980**, *36*, 227.

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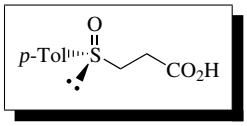
(*R*)-(+)-3-(*p*-Tolylsulfinyl)propionic Acid



[90334-31-9] $C_{10}H_{12}O_3S$ (MW 212.29)

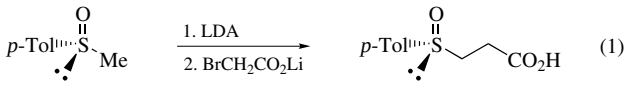
InChI = 1/C10H12O3S/c1-8-2-4-9(5-3-8)14(13)7-6-10(11)12/h2-5H,6-7H2,1H3,(H,11,12)/t14-/m1/s1/f/h11H

InChIKey = SAPXOXBQNHAYHL-TYNDYYKPDE

(asymmetric aldol-type condensation[2])

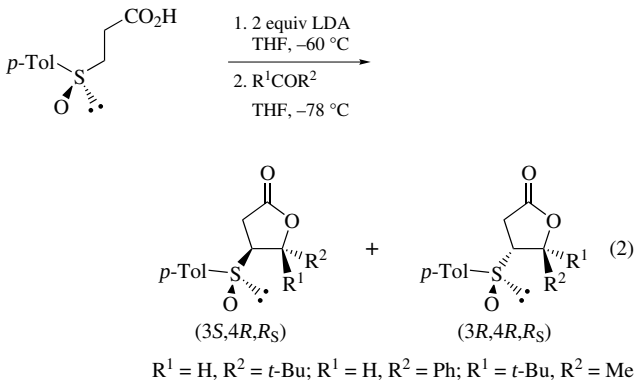
Physical Data: $[\alpha]_D$ = +180° ($CHCl_3$, *c* = 0.7), $[\alpha]_D$ = +188° (MeOH, *c* = 0.7).

Preparative Methods: conveniently prepared in 76% yield by addition of a suspension of lithium bromoacetate to a solution of the anion of (*R*)-(+)-methyl *p*-tolyl sulfoxide (eq 1).[1,2]



(1)

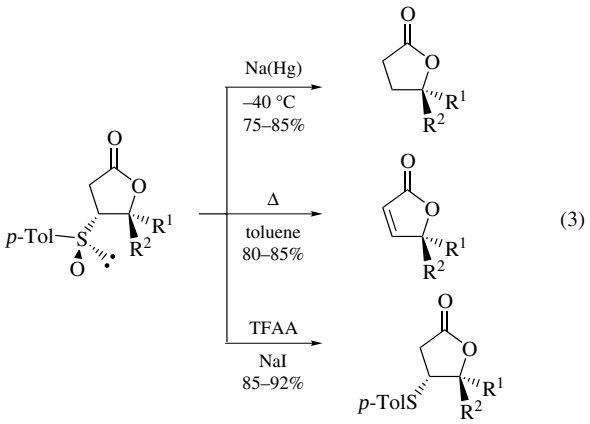
Aldol-type Condensation. Dimetalation of (*R*)-(+)-3-(*p*-tolylsulfinyl)propionic acid with lithium diisopropylamide produces a chiral homoenolate dianion equivalent which reacts with carbonyl compounds to afford β-sulfinyl-γ-hydroxy acids; these spontaneously cyclize to give the corresponding β-sulfinyl γ-lactones (eq 2).[1,2]



(2)

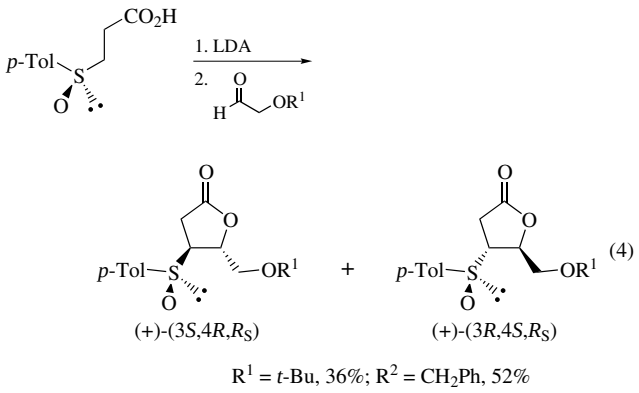
R^1 = H, R^2 = *t*-Bu; R^1 = H, R^2 = Ph; R^1 = *t*-Bu, R^2 = Me

Two new chiral carbon atoms are formed in the condensation and four diastereoisomeric β-sulfinyl γ-lactones can therefore in principle be obtained. However, only two diastereoisomers, (3*S*,4*R*,R_S) and (3*R*,4*S*,R_S), are isolated when the carbanion is condensed with pivalic aldehyde, benzaldehyde, or pinacolone (yield 65–70% for aldehydes, ratio 53:47; yield 47% for pinacolone, ratio 81:19). The diastereoselectivity decreases when the two substituents of the carbonyl group are sterically similar. However, single diastereoisomers can easily be separated through chromatography and transformed in high yield into both enantiomers of optically pure saturated (by desulfurization) and α,β-unsaturated γ-lactones (by pyrolytic sulfoxide elimination) (eq 3). The relative and absolute stereochemistry of all the products have been determined by circular dichroism, nuclear Overhauser effects, and X-ray analyses.



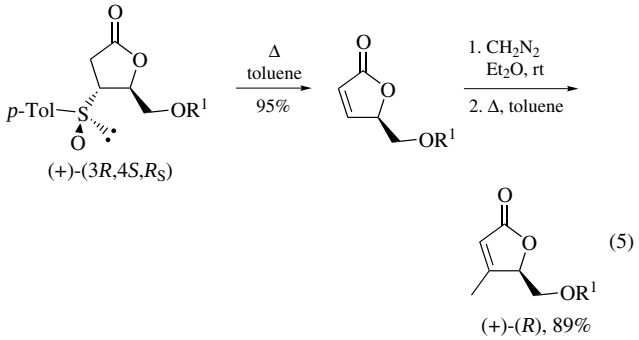
(3)

The condensation of the dilithio derivative of (*R*)-(+)-3-(*p*-tolylsulfinyl)propionic acid with protected glycoaldehydes (*O*-*t*-butyl and *O*-benzyl) gives 5-alkoxy-4-hydroxy-3-(*p*-tolylsulfinyl) pentanoic acids, which spontaneously cyclize to the corresponding 3-sulfinyl-4-alkoxymethyl butanolides (eq 4).[3] Pure diastereomers can be separated by flash chromatography and are obtained in comparable amounts. The corresponding optically pure butenolides are obtained by pyrolytic elimination of the sulfoxides and then transformed into natural (+)-(*R*)-umbelactone (eq 5).



(4)

R^1 = *t*-Bu, 36%; R^2 = CH_2Ph, 52%



(5)

1. Bravo, P.; Carrera, P.; Resnati, G.; Ticozzi, C., *J. Chem. Soc., Chem. Commun.* **1984**, 19.
2. Albinati, A.; Bravo, P.; Ganazolli, F.; Resnati, G.; Viani, F., *J. Chem. Soc., Perkin Trans. 1* **1986**, 1405.
3. Bravo, P.; Resnati, G.; Viani, F., *Gazz. Chim. Ital.* **1987**, *117*, 747.

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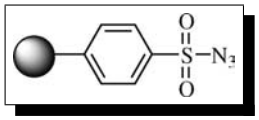
Tosyl Azide, Polymer-supported



[941-55-9]

(a cross-linked polystyrene (1% divinylbenzene) used as a reagent for diazo transfer to activated methylene groups)

Alternate Name: polystyrene-supported benzenesulfonyl azide, PS-TsA.

Physical Data: white polymer beads, 100–200 mesh, loading of 1.0–1.5 mmol/g, initiation temperature is 130 °C, onset temperature is 165.98 °C, peak exotherm is 192.72 °C, heat of decomposition is 0.27 cal/s/g, and BAM friction > 360 N.

Solubility: this is an insoluble polymer.

Form Supplied in: polystyrene-supported beads of 100–200 mesh and 1.0–1.5 mmol/g loading.

Analysis of Reagent Purity: Fourier transform infrared spectroscopy (FTIR), combustion analysis.

Preparative Methods: the title reagent[1] can be prepared in one step by the reaction of polystyrene-supported benzenesulfonyl chloride (100–200 mesh, available from Aldrich, 51,623-6 [163894-16-4], as 1% DVB cross-linked polystyrene resin with a loading of 1.5–2.0 mmol/g) with sodium azide (1.5 equiv) in DMF/H_2O (reaction complete at rt in 16 h).

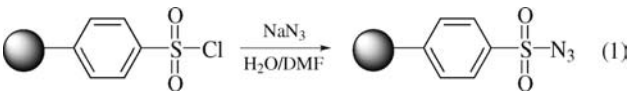
Purity: filter and wash with H_2O, DMF, and finally with CH_2Cl_2. Dry under vacuum at 40 °C.

Handling, Storage, and Precautions: PS-TsA is a relatively safe alternative to existing azide reagents; the reagent appears to be stable at room temperature (rt) over an indefinite period of time. Due to the toxicity and potentially explosive nature of diazo alkanes, proper precaution should be taken when using this and any other azide reagents. Disposal of azide-containing material was done in accordance with safe laboratory procedures.[2]

Diazo Transfer Reagent. Polystyrene-supported tosyl azide (PS-TsA) reagent for utilization as a diazo transfer reagent[3] has multiple advantages over traditional solution-phase azide reagents. The reagent is easily prepared in one step and offers the advantage of rapid isolation of the α-diazo product with no aqueous work up and in most cases no need for purification after filtration from the resin and removal of the solvent. Another advantage of PS-TsA, i.e., often improved yields with shorter reaction times, is comparable to 4-carboxybenzene sulfonazide (*p*-CBSA)[4] and other reported reagents.[5] It has been noted, with reagents such as *p*-CBSA and 4-acetamidobenzenesulfonyl azide (*p*-ABSA),[5] that the electron withdrawing effect of the functional group at the 4-position could possibly slow the rate of diazo transfer. The fact that the benzenesulfonyl azide of PS-TsA is attached directly to the carbon backbone of the polystyrene resin circumvents this problem, and could explain the shorter reaction times. Products using PS-TsA are obtained in a matter of a few hours at rt, at which time the starting material is consumed as evidenced by thin layer chromatography (TLC).

Another advantage of PS-TsA as a diazo transfer reagent is that the polystyrene-supported reagent is thermally stable and is not friction sensitive, which provides the reagent with improved process safety characteristics over the other available reagents. Examination of the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) traces of PS-TsA reveals that the decomposition occurs within a normal range. The DSC trace shows an initiation temperature of 130 °C with an onset temperature of 165.98 °C. The peak exotherm temperature reaches 192.72 °C (similar to that for *p*-CBSA of 190.0 °C) with a heat of decomposition of 65.6 cal/g. There is a significant difference (four-fold) in the maximum rate of energy released due to decomposition, which is approximately 275 J/g versus 1133 J/g for *p*-CBSA. The results of the BAM friction test[6] indicate that the limiting impact energy for PS-TsA is greater than 360 N [friction sensitivity (BAM friction test) was performed by Chilworth Technology, Inc. Princeton, NJ]. These observations and the fact that the parent benzenesulfonyl azide is not observed to be shock sensitive[7] indicate a favorable safety profile at low concentrations. PS-TsA safety data also compares favorably to safety data reported on other arylsulfonyl azides.[8]

Preparation. The PS-TsA (eq 1) is prepared in one step from polystyrene-supported benzenesulfonyl chloride (100–200 mesh, 1.5–2.0 mmol/g). Typically, 1.5 mmol of resin is swollen in DMF and then treated with 3.0 mmol of NaN_3 dissolved in H_2O (1.0 mL) and diluted with DMF (7 mL). After 16 h the resin is washed with H_2O (5 × 5 mL), DMF (5 × 5 mL), and finally with CH_2Cl_2 (3 × 5 mL) and dried under vacuum at 40 °C. The loading of PS-TsA was determined to be 1.0–1.5 mmol/g by combustion analysis of two different batches. The resin is stored at rt and appears to be stable over an indefinite period of time. FTIR of the resin shows a strong band for the azide functionality at 2130 cm^{-1}.



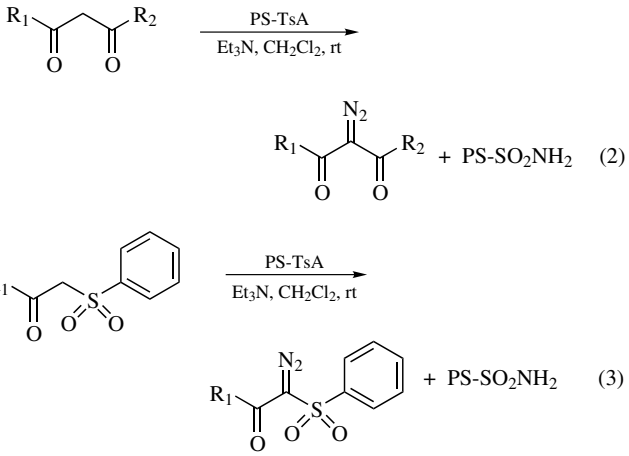
(1)

Diazo Transfer Reaction.

General Procedure for Diazo Transfer Using Polystyrene-supported Tosyl Azide. PS-TsA (0.75 mmol) was placed in a 5.0-mL disposable polypropylene syringe and was swollen with CH_2Cl_2. A mixture of activated methylene compound (0.5 mmol) and Et_3N (1.5 mmol) in CH_2Cl_2 (2.0 mL) was drawn into the syringe containing the resin, placed on a LabQuake shaker, and was then rotated at rt. The reaction progress was monitored by TLC. After 4 h, the supernatant was collected and the resin was washed with CH_2Cl_2 (3 × 5 mL). The washes were combined with the supernatant, and concentrated to give the α-diazo carbonyl product that was reasonably pure as shown by nuclear magnetic resonance.

Although azide reagents have been utilized in a number of chemical transformations,[9] to date PS-TsA has only been utilized for the direct transfer of a diazo function to methylene groups flanked by either two carbonyls (eq 2), a carbonyl and an aryl sulfonyl (eq 3), or the methylene of 10*H*-anthracen-9-one. Diazodicarbonyl compounds such as 5-diazo-2,2-dimethyl-[1,3]dioxane-4,6-dione, 2-diazo-3-oxo-butyric acid ethyl ester, 10-diazo-10*H*-anthracen-9-one, 2-diazo malonic acid diethyl ester, and 2-diazo-3-oxo-butyric acid *tert*-butyl ester, as well as

2-benzenesulfonyl-2-diazo-1-phenylethanone, were readily prepared from the corresponding methylene compound in good yields (63–98%).[1] Other uses for PS-TsA have yet to be explored.



Related Reagents. Methanesulfonyl Azide (MsN_3); *p*-Toluenesulfonyl Azide (*p*-TSA); *p*-Acetamidobenzenesulfonyl Azide (*p*-ABSA); 4-Carboxybenzenesulfonylazide (*p*-CBSA); *p*-Dodecylbenzenesulfonyl Azide.

1. Green, G. M.; Peet, N. P.; Metz, W. A., *J. Org. Chem.* **2001**, *66*, 2509.
2. In *Prudent Practices for Disposal of Chemicals from Laboratories*, National Research Council, Committee on Hazardous Substances in the Laboratory, National Academy Press, Washington, D.C., 1983, p 87.
3. Regitz, M.; Hocker, J.; Liedhegener, A., *Org. Synth. Coll.* **1973**, *5*, 179.
4. Hendrickson, J. B.; Wolf, W. A., *J. Org. Chem.* **1968**, *33*, 3610.
5. Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D., *Synth. Comm.* **1987**, *17*, 1709.
6. Balabanov, G. P.; Dergunov, Y. I., *Zh. Prikl. Khem.* (Leningrad) **1968**, *41*, 2578.
7. In *Bretherick's Handbook of Reactive Chemical Hazards, 5th Ed.*, Urben, P. G., Ed.; Butterworth-Heinemann: Oxford, 1995, Vol. 1, p 752.
8. Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W., *Synth. Comm.* **1981**, *11*, 947.
9. (a) Padwa, A.; Sheehan, S. M.; Straub, C. S., *J. Org. Chem.* **1999**, *64*, 8648. (b) Kettle J. G.; Faull, A. W.; Fillery, S. M.; Flynn, A. P.; Hoyle, M. A.; Hudson, J. A., *Tetrahedron Lett.* **2000**, *41*, 6905. (c) Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T., *Org. Lett.* **1999**, *1*, 383. (d) Whitehouse, D. L.; Nelson, K. H., Jr; Savinov, S. N.; Austin, D. J., *Tetrahedron Lett.* **1997**, *38*, 7139. (e) Gowravaram, M. R.; Gallop, M. A., *Tetrahedron Lett.* **1997**, *38*, 6973. (f) Prein, M.; Padwa, A., *Tetrahedron Lett.* **1996**, *37*, 6981. (g) Padwa, A.; Austin, D. J., *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797. (h) Cox, G. G.; Moody, C. J.; Austin, D. J.; Padwa, A., *Tetrahedron* **1993**, *49*, 5109.

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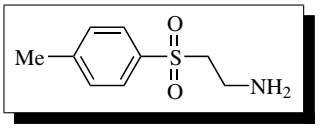
Aventis Pharmaceuticals, Bridgewater, NJ, USA

β-Tosylethylamine

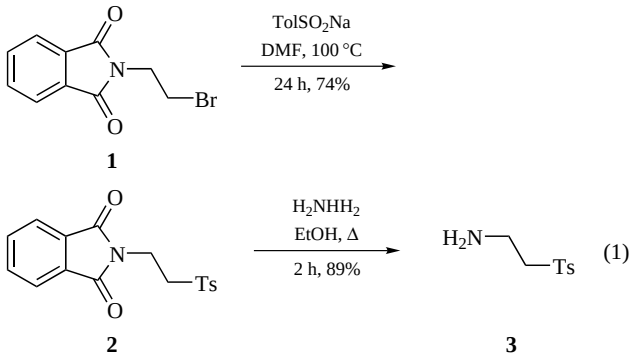


[50702-03-9] $C_8H_{13}NO_2S$ (MW 199.27)
InChI = 1/C9H13NO2S/c1-8-2-4-9(5-3-8)13(11,12)7-6-10/h2-5H,6-7,10H2,1H3
InChIKey = CQTYBCCVEBZJEX-UHFFFAOYAA

(a masked ammonia equivalent)

Physical Data: mp 62.5–64 °C; colorless solid; recrystallized from benzene-hexanes (~3:1).
Solubility: soluble in most organic solvents.
Form Supplied in: not commercially available.
Handling, Storage, and Precautions: stable to air and moisture. Toxicological properties unknown; assumed to be toxic.

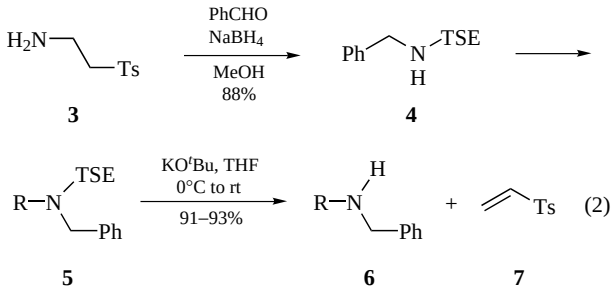
Preparation. β-Tosylethylamine (TSE-NH_2) (**3**) is prepared via a two-step sequence from commercially available starting materials (eq 1).[1] Treatment of *N*-(2-bromoethyl)phthalimide (**1**) with the sodium salt of *p*-toluenesulfinic acid in DMF at 100 °C produces β-tosylethylphthalimide (**2**) in 74% yield. Cleavage of the phthalimide protecting group from **2** using hydrazine in refluxing ethanol liberates β-tosylethylamine (**3**) in 89% yield.



A Masked Ammonia Equivalent. Weinreb and co-workers described the utility of **3** as an ammonia synthon.[1] TSE-NH_2 (**3**) was reductively alkylated with benzaldehyde in the presence of $NaBH_4$ to afford secondary amine **4**, which was subsequently *N*-acylated or *N*-sulfonylated to generate TSE amido compounds such as **5** (eq 2). Removal of the TSE group from **5** was achieved via a β-elimination using potassium *t*-butoxide to afford **6** and vinyl sulfone (**7**), which polymerizes under these conditions.

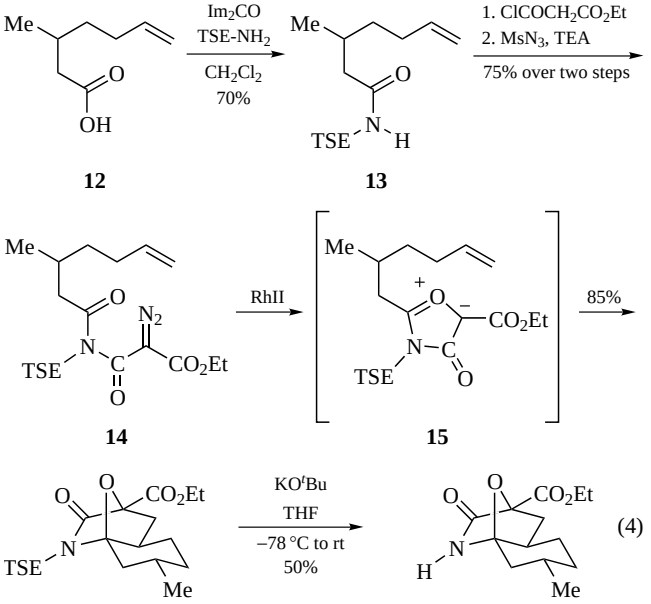
Applications of β-Tosylethylamine. Borzilleri and Weinreb used TSE amine (**3**) in an imino-ene cyclization for the total synthesis of (−)-papuamine.[2] Exposure of the allenylsilane aldehyde **8** to amine **3** in the presence of $SnCl_4$ or under thermal conditions generates the corresponding imine, which undergoes stereospecific cyclization to afford the TSE aminoalkyne **9** following work-up with TBAF (eq 3). The aminoalkyne **9** was converted to the

bis-TSE acetamide **10** via several steps at which point the TSE groups were cleaved using potassium *t*-butoxide to afford the bis-amide **11**.



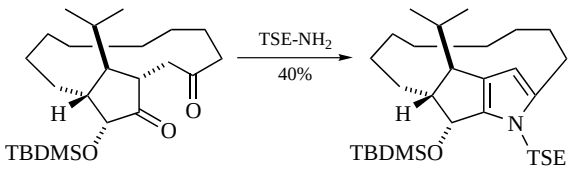
3 **4** **5** **6** **7** (2)

TSE-NH_2 (**3**) has been utilized for the formation of 1,3-dipoles.[3] Thus, treatment of **3** with the *N*-acyl imidazole derived from the carboxylic acid **12** generated the TSE amide **13**, which was acylated and diazotized to yield the diazo amide **14** (eq 4). Exposure of intermediate **14** to a Rh(II) catalyst produced isomünchnone (**15**), which participated in an intramolecular [3 + 2] cycloaddition to afford the bridged bicycle **16** in 85% yield. Subsequent removal of the TSE protecting group using potassium *t*-butoxide afforded the lactam **17** in 50% yield.

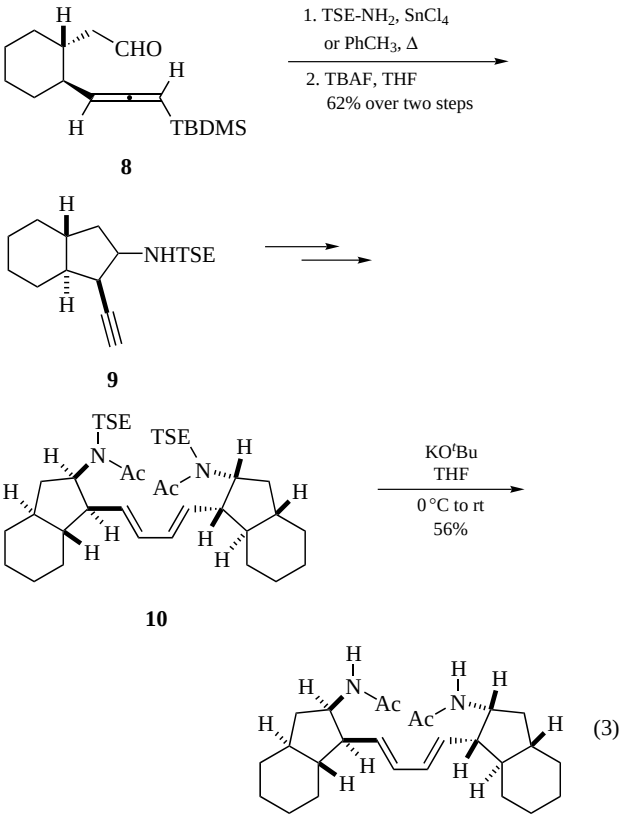


12 **13** **14** **15** **16** **17** (4)

β-Tosylethylamine (**3**) has also been employed for the preparation of the pyrrole moiety found in rosephilin.[4] Treatment of the diketone **18** with amine **3** affords the TSE protected pyrrole **19**, albeit in only 40% yield (eq 5).



18 **19** (5)



8 **9** **10** **11** (3)

1. DiPietro, D.; Borzilleri, R. M.; Weinreb, S. M., *J. Org. Chem.* **1994**, *59*, 5856.
2. Borzilleri, R. M.; Weinreb, S. M.; Parvez, M., *J. Am. Chem. Soc.* **1995**, *117*, 10905.
3. Brodney, M. A.; Padwa, A., *J. Org. Chem.* **1999**, *64*, 556.
4. Trost, B. M.; Doherty, G. A., *J. Am. Chem. Soc.* **2000**, *122*, 3801.

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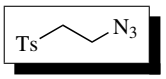
β-Tosylethylazide



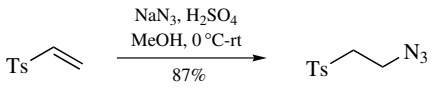
[889095-73-2] $C_9H_{11}N_3O_2S$ (MW 225.27)

InChI = 1/C9H11N3O2S/c1-8-2-4-9(5-3-8)15(13,14)7-6-11-12-10/h2-5H,6-7H2,1H3

InChIKey = GHKHCLPDHSKVTM-UHFFFAOYAF

(a useful reagent for the preparation of *N*-protected triazoles)

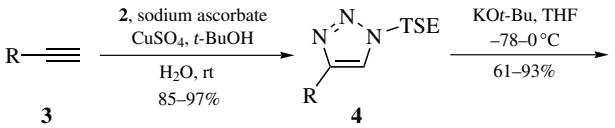
Physical Data: white crystalline solid.
Solubility: sol in most organic solvents.
Form Supplied in: not commercially available.
Preparative Methods: β-tosylethylazide (TSE-N_3) (**2**) is easily obtained in one step in good yield from the reaction of commercially available tosyl vinyl sulfone (**1**) and sodium azide/sulfuric acid in methanol (eq 1).[1]



1 **2** (1)

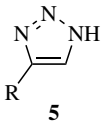
Handling, Storage, and Precautions: handle with care like other alkyl azides due to the potential for explosions from shock or heat. Use in a fume hood. Storage under a nitrogen atmosphere and in a refrigerator is recommended.

Reaction with Terminal Alkynes to Give 4- or 5-Substituted *N*-Protected Triazoles. Using the Sharpless protocol,[2] treatment of TSE-N_3 (**2**) with terminal alkynes **3** in the presence of cupric sulfate/sodium ascorbate in aqueous *tert*-butanol at room temperature gives the 4-substituted-1,2,3-triazoles **4** in good to excellent yields (eq 2).[1] The TSE protecting group can be removed by treatment of **4** with potassium *tert*-butoxide in THF to give free triazoles **5** along with vinyl sulfone **1**, which polymerizes under the reaction conditions.



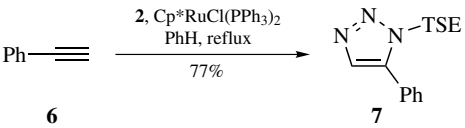
3 **4**

R = alkyl, aryl
TSE = CH_2CH_2Ts



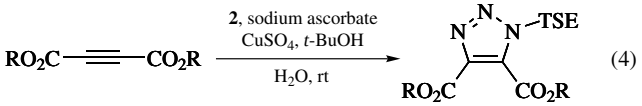
5 + **1** (2)

The ruthenium(I) catalyzed conditions developed by the Sharpless group[3] can also be used for the cycloaddition of TSE-N_3 (**2**) and terminal alkyne **6** to give 5-substituted triazole **7** with reversed regiochemistry relative to adducts **4** (eq 3).[1]



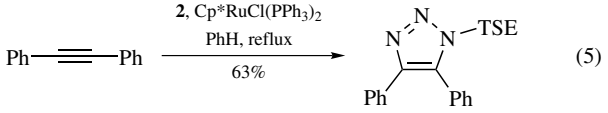
6 **7** (3)

Reaction with Internal Alkynes to Give 4, 5- Disubstituted *N*-Protected Triazoles. The cycloaddition of TSE-N_3 (**2**) with internal alkynes is facilitated by both the Cu(I) and Ru(I) catalytic systems. Treatment of symmetrical alkynes **8**, **9** with azide **2** using Cu(I) catalysis affords 4,5-disubstituted triazoles **10**, **11** respectively, in good yields (eq 4).[1] Similarly, Ru(I) catalyzed cycloaddition of symmetrical alkyne **12** provides triazole **13** in moderate yield (eq 5).[1]



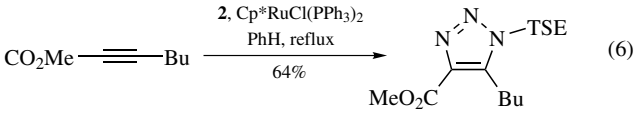
8 R= H
9 R= Me

10 R= H 75%
11 R= Me 86% (4)



12 **13** (5)

Using the Ru(I) catalytic system, cycloaddition of TSE-N_3 (**2**) and unsymmetrical internal alkyne **14** provides 4,5-disubstituted triazole **15** as a single regioisomer in 64% yield (eq 6).[1]



14 **15** (6)

1. Yap, A. H.; Weinreb, S. M., *Tetrahedron Lett.* **2006**, *47*, 3035.
2. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B., *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
3. Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G., *J. Am. Chem. Soc.* **2005**, *127*, 15998.

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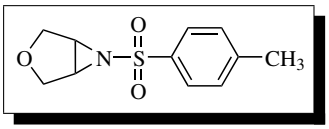
6-Tosyl-3-oxa-6-azabicyclo[3.1.0]hexane



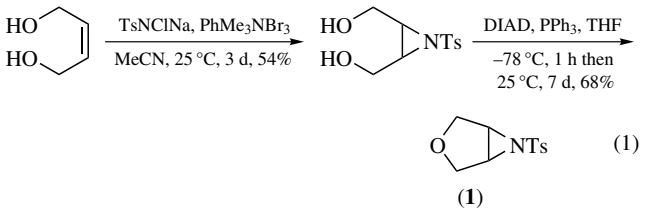
[798575-96-9] $C_{11}H_{13}NO_3S$ (MW 239.29)
InChI = 1/C11H13NO3S/c1-8-2-4-9(5-3-8)16(13,14)12-10-6-15-7-11(10)12/h2-5,10-11H,6-7H2,1H3
InChIKey = OJDZWLMBZRFJOU-UHFFFAOYAG

(reagent used to prepare unsaturated 1,2-amino alcohols[1] and alkynyl 1,2-amino alcohols[2])

Physical Data: white solid;[2] mp 117–117.5 °C;[3] mp 96–98 °C.[2]
Solubility: THF, Et_2O.
Preparative Methods: compound (**1**) can be prepared in two steps as shown in eq 1; first aziridination of *cis*-but-2-ene-1,4-diol (1 equiv) is done with TsNClNa (1.1 equiv) and $PhMe_3NBr_3$ (0.1 equiv) in acetonitrile at 25 °C for 3 days. This is followed by treatment of the diol with diisopropyl azodicarboxylate (DIAD, 1.5 equiv) and PPh_3 (1.5 equiv) in THF at −78 °C for 1 h followed by stirring at 25 °C for 7 days.[1]

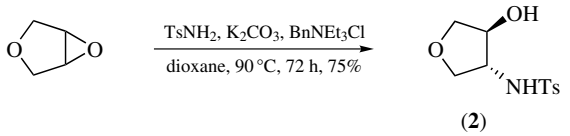
A cognate procedure (eq 2) that is more efficient in yield and time begins with the ring opening of 2,5-dihydrofuran epoxide (50 mg, 1 equiv) by heating with *p*-toluenesulfonamide

(119 mg, 1.2 equiv), K_2CO_3 (8 mg, 0.1 equiv), and $BnEt_3N^+Cl^-$ (13 mg, 0.1 equiv) in dioxane (0.3 mL) for 72 h at 90 °C, giving the hydroxy sulfonamide (**2**) in a 75% yield. This is followed by treatment of **2** (570 mg, 1 equiv) with pyridine (0.96 mL, 5.1 equiv) and MsCl (0.88 mL, 5.1 equiv) in CH_2Cl_2 (25 mL) and then heating at reflux for 16 h. After cooling to room temperature, the reaction mixture is washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give the intermediate mesylate (not shown). The cyclization to give **1** is performed by stirring the crude mesylate with K_2CO_3 (1.20 g, 4 equiv) in acetonitrile (25 mL) for 16 h at 45 °C. Aqueous workup and purification gives **1** (74%).[2]

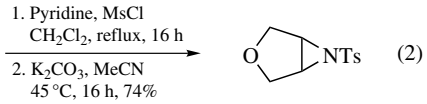


(1)

(**1**)



(**2**)



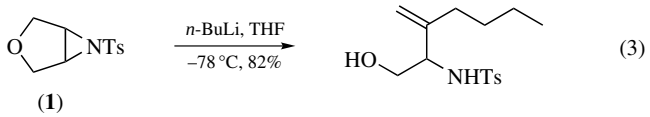
(2)

(**1**)

Purification: compound **1** can be purified by column chromatography on silica gel eluting with 30–100% Et_2O in light petroleum ether[1] or by eluting with petroleum ether/EtOAc (9:1).[2]

Handling, Storage, and Precautions: recommend storage at 4 °C.

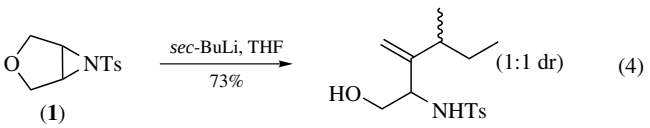
Unsaturated 1,2-Amino Alcohols. The synthesis of unsaturated 1,2-amino alcohols (eqs 3–12) offers the potential of preparing a variety of unsaturated α-amino acids by the method of Flock et al., where Jones oxidation of the alcohol and removal of the toluenesulfonyl nitrogen protecting group under acidic conditions would give an α-amino acid.[4] The unsaturated 1,2-amino alcohol functionality has been used in the synthesis of bicyclic bisarylimidazole derivatives.[5] An initial investigation into the formation of unsaturated 1,2-amino alcohols by reacting **1** with an organolithium reagent gave the nitrogen-protected unsaturated amino alcohol after optimization of conditions in 82% yield when treated with a solution of *n*-BuLi (3 equiv) in THF at −78 °C (eq 3).[1] The formation of the unsaturated 1,2-amino alcohol (eq 3) is initiated by α-lithiation of the aziridine in **1** followed by *n*-BuLi insertion into the α-lithiated aziridine and elimination with loss of the alkoxide giving the unsaturated amino alcohol after an aqueous workup.[1]



(3)

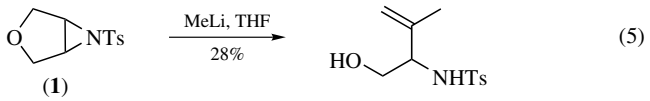
(**1**)

From this initial work, series of unsaturated 1,2-amino alcohols were prepared from **1** using a variety of organolithium reagents, including branched alkyl, vinyl, aryl, and heteroaryl organolithiums.[1,3] As shown in eqs 4–12, all of the organolithium reagents used gave the expected unsaturated 1,2-amino alcohols in reasonable yields (42–80%) except for methyllithium that gave the amino alcohol in 28% yield. It must be noted that in this initial study no attention to the stereochemistry of the carbon center bearing the nitrogen and the unsaturated alkyl is discussed.[1]



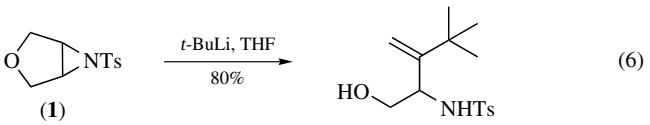
(4)

(**1**)



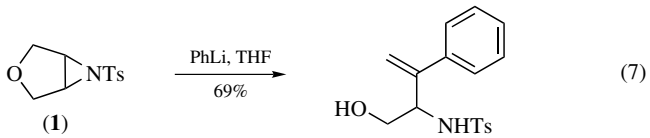
(5)

(**1**)



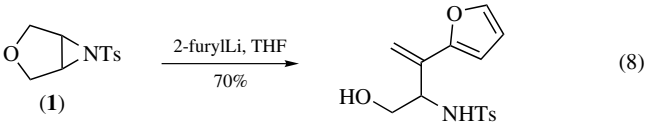
(6)

(**1**)



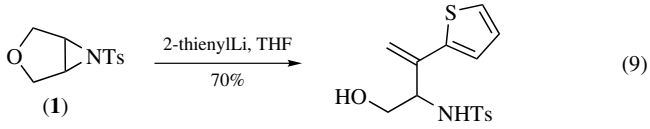
(7)

(**1**)



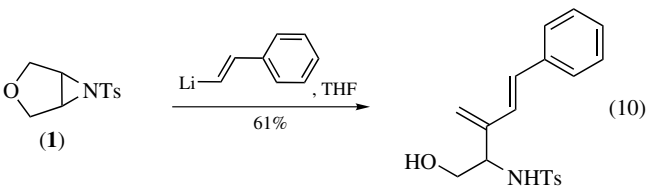
(8)

(**1**)



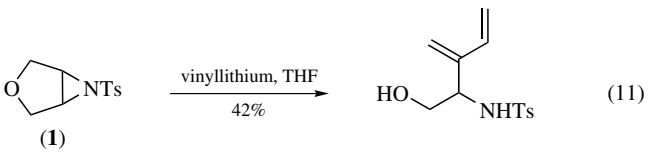
(9)

(**1**)



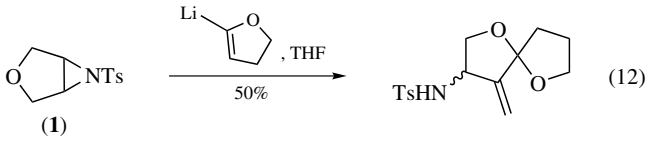
(10)

(**1**)



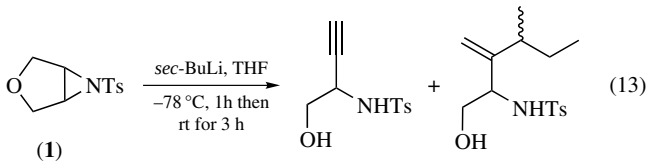
(11)

(**1**)



(**1**) (12)

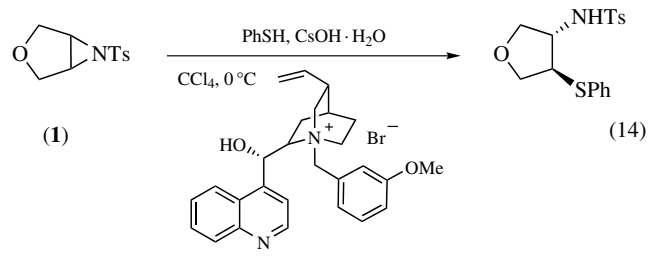
Alkynyl Amino Alcohols. Compound **1** can be used to prepare alkynyl amino alcohols; when the alkyllithium reagent used is *sec*-BuLi (3 equiv) a mixture of the *N*-protected alkynyl amino alcohol and the *N*-protected amino alcohol is obtained (21 and 55%, respectively, eq 13).[6] It is noteworthy that the authors of this article were able to optimize the yield of the alkynyl amino alcohol by the addition of pentamethyldiethylenetriamine (PMDETA) and the use of *N*-2,4,6-triisopropylbenzenesulfonyl over the *N*-toluenesulfonyl nitrogen protecting group.[6]



(**1**) 21% 55% (13)

Asymmetric Ring Opening. A later study by Hodgson et al. attempted to use (−)-sparteine as a chiral auxiliary ligand with *n*-BuLi (3 equiv) in an attempt to drive an enantioselective desymmetrization of **1** to the desired unsaturated 1,2-amino alcohol.[3] This only led to isolation of the starting material **1** and $TsNH_2$, or with prolonged reaction times consumption of **1** was achieved but only to give $TsNH_2$ and the alkynyl amino alcohol as in eq 13. To achieve the enantioselective synthesis of an unsaturated amino alcohol, the conversion of L-tartaric acid to an acyclic form of **1** and treatment with an alkyl lithium (e.g., *n*-BuLi) gave the desired enantiomerically pure unsaturated amino alcohol in 70% yield.[3]

There is only one example of an enantioselective desymmetrization by nucleophilic ring opening of **1** where a chiral auxiliary ligand was used. As shown in eq 14, the use of an ammonium salt of a cinchona alkaloid afforded the ring opening of **1** with thiophenol, giving a high yield of the opened product (92%) with some enantioselectivity (44% ee).[7]



(**1**) (14)

1. Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J., *Chem. Commun.* **2004**, 2234.
2. Huang, J. H.; O'Brien, P., *Synthesis* **2006**, 425.
3. Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J., *J. Org. Chem.* **2006**, *71*, 8510.
4. Flock, S.; Frauenrath, H., *Synlett* **2001**, 839.
5. Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A., *J. Am. Chem. Soc.* **2007**, *129*, 490.
6. Huang, J.; O'Brien, P., *Chem. Commun.* **2005**, 5696.
7. Luo, Z.-B.; Hou, X.-L.; Dai, L.-X., *Tetrahedron: Asymmetry* **2007**, *18*, 443.

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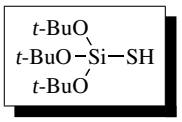
Tri(*tert*-butoxy)silanethiol



[690-52-8] $C_{12}H_{28}O_3SSi$ (MW 280.50)

InChI = 1/C12H28O3SSi/c1-10(2,3)13-17(16,14-11(4,5)6)15-12(7,8)9/h16H,1-9H3

InChIKey = ZVUGYOCGLCLJAV-UHFFFAOYAF

(reagent used as an efficient hydrogen donor and catalyst in the context of polarity reversal catalysis in radical chain reactions)

Alternate Name: TBST.

Physical Data: bp 113–115 °C/35 mmHg);[1] 95 °C/15 mmHg.[2]

Solubility: soluble in common organic solvents.

Form Supplied: colorless liquid, not commercially available.

Analysis of Reagent Purity: the reagent may be checked by bp or analyzed by ^1H NMR spectroscopy.

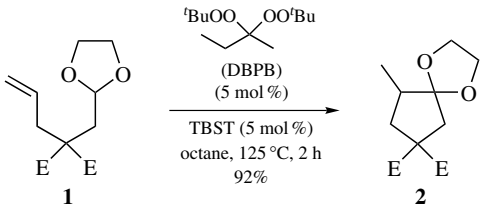
Preparative Method: this reagent can be prepared by alcoholysis of silicon disulfide (SiS_2).[1,2] Representative procedure: powdered silicon disulfide (95% pure; 20.2 g, 0.21 mol) was charged into a 100 ml round-bottomed flask containing a robust stirrer bar and equipped with a reflux condenser. *tert*-Butyl alcohol (60.0 g, 0.81 mol) was added and the mixture was stirred and heated under reflux under nitrogen for 72 h. The cooled reaction mixture was filtered through Celite to remove unreacted silicon disulfide and the filter cake was washed with diethyl ether. Excess of alcohol and diethyl ether were removed from the filtrate by rotary evaporation and the residual oil was distilled under reduced pressure to give the silanethiol (18.1 g, 31%) as a colorless liquid, bp 95 °C/15 mmHg, 113–115 °C/35 mmHg).

Purification: this reagent may be purified by distillation.

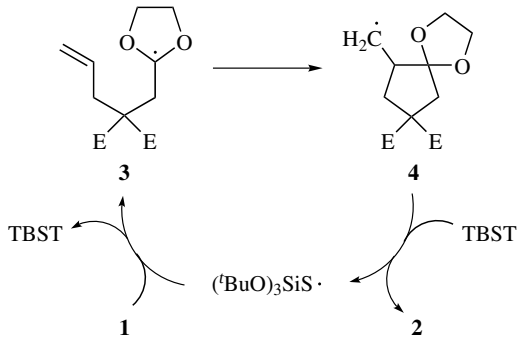
Handling, Storage, and Precautions: thiols are known to be susceptible to autooxidation. This reagent may be toxic and may possess an unpleasant order. It should be kept under an inert atmosphere and handled with care.

Thiol-catalyzed Radical-chain Cyclization of Unsaturated Acetals and Thioacetals. When the unsaturated dioxolane **1** and a radical initiator, 2,2-di(*t*-butylperoxy)butane (DBPB), were heated at 125 °C in octane in the presence of tri(*t*-butoxy) silanethiol (TBST), the spirocyclic ketal **2** was formed cleanly and isolated in 92% yield (eq 1).[3] When the reaction was performed in the absence of TBST, compound **2** was not detected. TBST is

believed to promote the generation of the 1,3-dioxolan-2-yl radical **3** by hydrogen-atom abstraction from **1** in a process termed polarity-reversal catalysis [4] (eq 2).

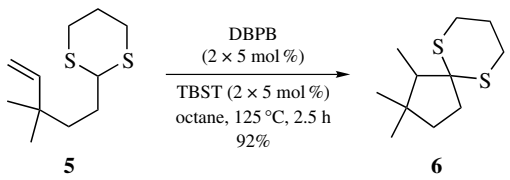


(1)



(2)

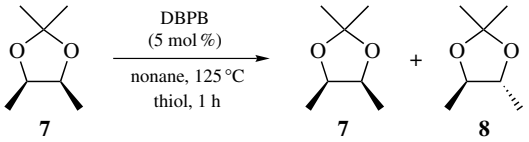
In the same context, TBST effectively catalyzes the cyclization of the unsaturated 1,3-dithiane **5** to give the cyclized product **6** in excellent yield (eq 3).



(3)

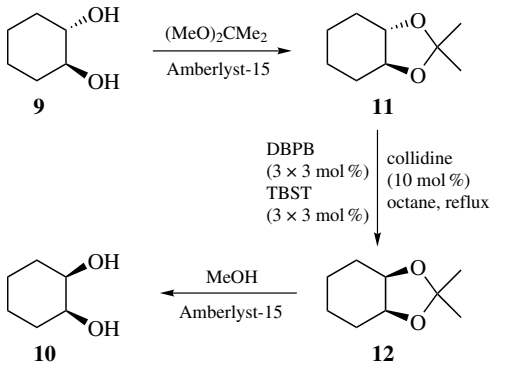
Selective Radical-chain Epimerization at C–H Bonds. When heated to 125 °C in a hydrocarbon solvent in the presence of a thiol as the catalyst and DBPB as initiator, the *cis*-cyclic ketal **7** underwent selective epimerization at the C–H center α to oxygen to give the thermodynamically more stable *trans*-epimer **8**. Silanethiols were found to be more effective protic-polarity reversal catalysts than alkanethiols (eq 4).[5] Thus, in the presence of TBST and a small amount of collidine as the scavenger of adventitious acid formed under the reaction conditions, the epimerization of **7** proceeded smoothly to give **8** in 84% conversion after 1 h. Interestingly, when triphenylsilanethiol was used as the catalyst, the coadministration of collidine proved to be detrimental, resulting in a suppression of the isomerization. This is probably because this latter thiol is susceptible to nucleophilic attack by the base. The improved performance of TBST is therefore attributed to its stability toward nucleophilic substitution at the silicon center.

In a sequence of derivatization, epimerization, and deprotection, the thermodynamically more stable *trans*-diol **9** was transformed to the less stable *cis*-isomer **10** through an efficient **11**→**12** epimerization (95% conversion) catalyzed by TBST (eq 5).[6]



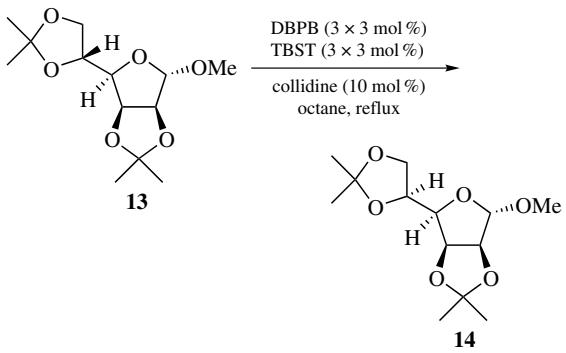
(4)

tert-$C_{12}H_{25}SH$	63:37
+ collidine (10 mol %)	
Ph_3SiSH	24:76
TBST (5 mol %)	16:84
+ collidine (10 mol %)	



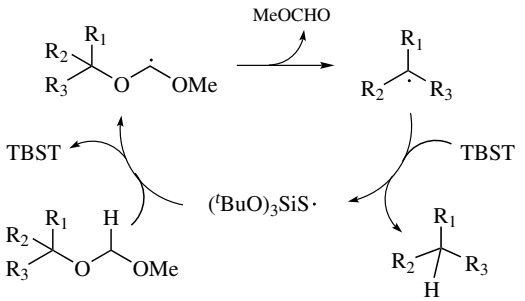
(5)

Cyclic ketals derived from carbohydrates also undergo synthetically useful thiol-catalyzed epimerization. For example, the α-D-mannofuranoside (**13**) was epimerized selectively at C-5 to give the β-L-gulofuranoside (**18**) in 30% conversion and 24% isolated yield (eq 6).[6]

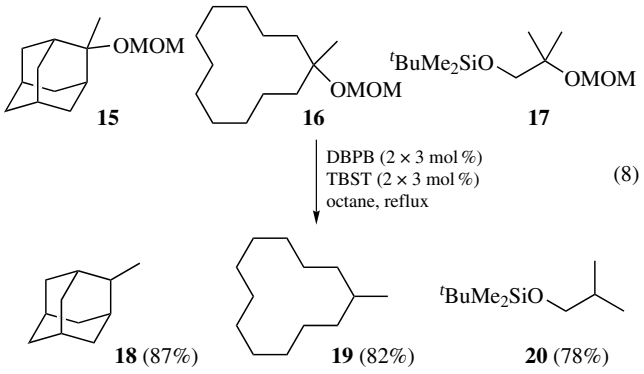


(6)

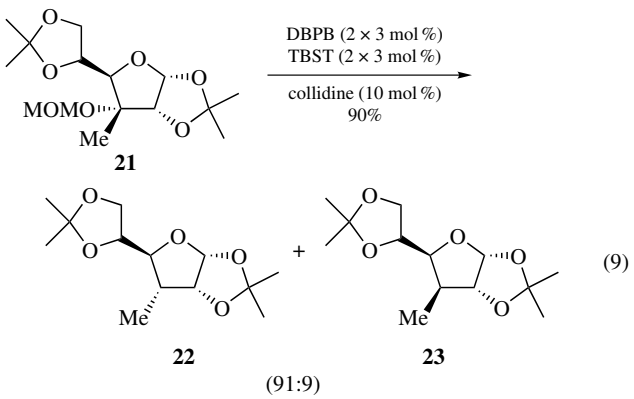
Radical-chain Deoxygenation of Tertiary Alcohols. As outlined by the general reaction scheme in eq 7, methoxymethyl (MOM) ethers derived from tertiary alcohols undergo TBST-mediated deoxygenative cleavage to form hydrocarbon products.[7] For example, when MOM ethers **15–17** were treated with DBPB in the presence of TBST and collidine in refluxing octane, the deoxygenation products **18–20** were isolated in high yields (eq 8).



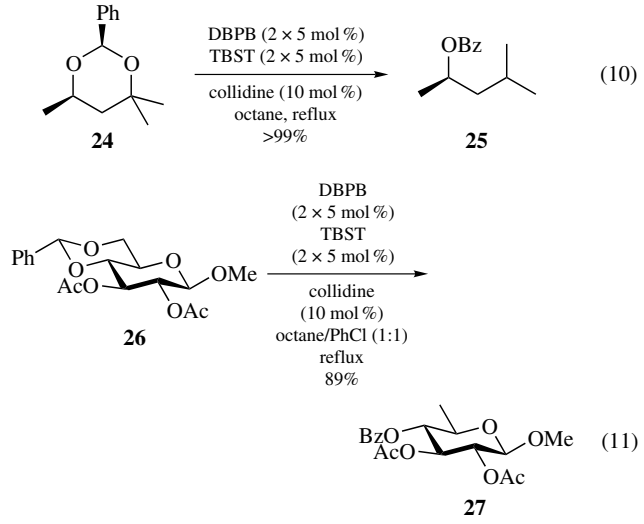
(7)



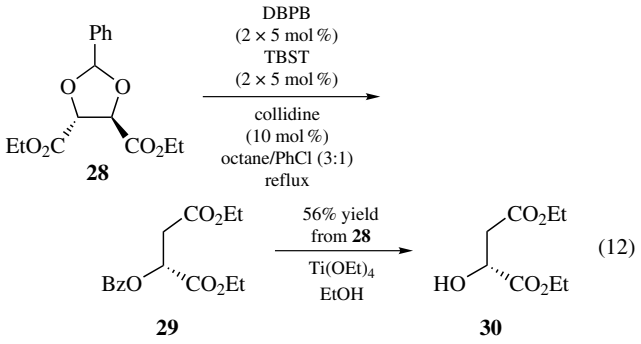
When the tertiary MOM ether **21**, which can be prepared from diacetone D-glucose, was subject to this polarity-reversal-catalysis protocol, the deoxygenated products **22** and **23** were isolated in excellent yield (90%) and good diastereoselectivity (91:9) (eq 9).[7]



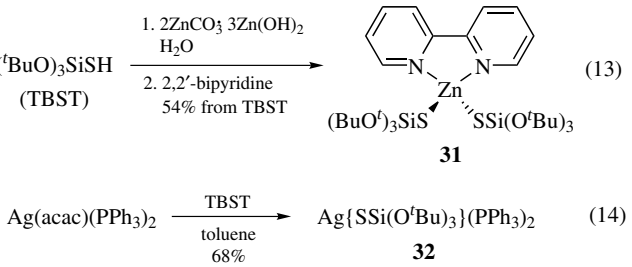
Radical-chain Redox Rearrangement of Cyclic Acetals. Benzylidene acetals of diols undergo radical-chain cleavage to give benzoate esters via the formation and subsequent selective fragmentation of a di(α-alkoxyl)benzyl radical.[8] Thus, cyclic acetal **24** was quantitatively converted to benzoate **25** under the catalysis of TBST (eq 10). Application to the carbohydrate derived cyclic acetal **26** led to the formation of the 6-deoxy glycoside **27** in high yield (eq 11).[8,9]



This chemistry has been successfully applied to the conversion of the tartaric acid derived acetal **28** to the ester derivative **30** of the unusual (*R*)-malic acid (eq 12).[8]



Other Applications. TBST is widely used as a thiolate ligand for the synthesis of various metal thiolates as exemplified by the formation of Zn(II) thiolate **31** (eq 13)[10] and silver(II) complex **32** (eq 14).[11]



Related Reagents. Triisopropylsilanethiol (TIPST); Triphenylsilanethiol (TPST).

1. Piekos, R.; Wojnowski, W., *Z. Anorg. Allg. Chem.* **1962**, *318*, 212.
2. Dang, H.-S.; Roberts, B. P.; Tocher, D. A., *J. Chem. Soc., Perkin Trans. 1* **2001**, 2452.
3. Dang, H.-S.; Roberts, B. P., *Tetrahedron Lett.* **1999**, *40*, 8929.
4. Roberts, B. P., *Chem. Soc. Rev.* **1999**, *28*, 25.
5. Dang, H.-S.; Roberts, B. P., *Tetrahedron Lett.* **1999**, *40*, 4271.
6. Dang, H.-S.; Roberts, B. P., *Tetrahedron Lett.* **2000**, *41*, 8595.
7. Dang, H.-S.; Franchi, P.; Roberts, B. P., *Chem. Commun.* **2000**, 499.
8. Roberts, B. P.; Smits, T. M., *Tetrahedron Lett.* **2001**, *42*, 137.
9. Dang, H.-S.; Roberts, B. P.; Sekhon, J.; Smits, T. M., *Org. Biomol. Chem.* **2003**, *1*, 1330.
10. Becker, B.; Radacki, K.; Wojnowski, W., *J. Organomet. Chem.* **1996**, *521*, 39.
11. Chojnacki, J.; Becker, B.; Konitz, A.; Potrzebowski, M.; Wojnowski, W., *J. Chem. Soc., Dalton Trans.* **1999**, 3063.

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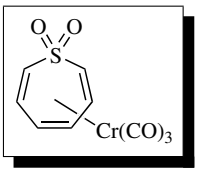
Tricarbonyl[(2,3,4,5,6,7-η)-thiepin-1,1-dioxide]chromium(0)[1]



[1452247-44-5] $C_9H_6CrO_5S$ (MW 278.201)

InChI = 1/C6H6O2S.3CO.Cr/c7-9(8)5-3-1-2-4-6-9;3*1-2;/h1-6H;;;;

InChIKey = OCEVGPRCNDLBNT-UHFFFAOYAQ

(reagent used for promotion of [6+2], [6+4], [6+2+2], and [6+2+2+2] higher-order cycloaddition reactions)

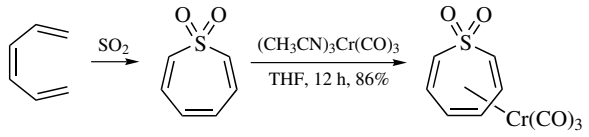
Physical Data: red solid; mp 173–174 °C.

Solubility: THF, ethyl acetate, CH_2Cl_2, $CHCl_3$, and 1,2-dichloroethane.

Form Supplied in: prepared from thiepin-1,1-dioxide and trisacetonitriletricarbonylchromium.

Purity: flash column chromatography on silica gel using hexanes/ethyl acetate.

Preparative Methods: as shown below, thiepin chromium complex **1** is readily prepared via standard methods[1] from thiepin-1,1-dioxide[2] **2** and trisacetonitriletricarbonylchromium(0)[3] **3**. The reaction proceeds in 12 h at room temperature to give an 86% yield of the desired chromium complex 1 (eq 1).[4]



(1)

2 **1**

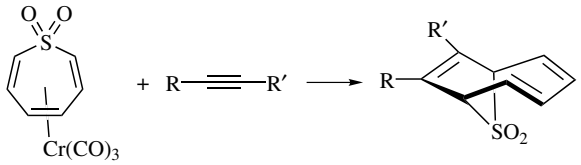
Handling, Storage, and Precautions: the compound can be handled in air and is generally stable for several months when stored in the freezer.

[6 + 2] Higher-order Cycloaddition Reactions. Chromium complex **1** undergoes a variety of higher-order cycloaddition reactions.[5] Thus, a reaction between complex **1** and disubstituted alkyne partners in the presence of UV light (uranium filter) produces [6π + 2π] cycloadducts in good yields (eq 2, Table 1). Cyclooctyne (entry 5, Table 1) notably provides an 80% yield of the cycloadduct.[6]

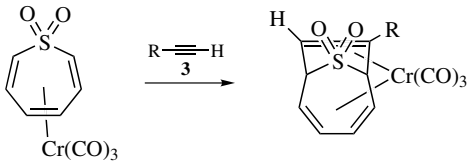
Surprisingly, unlike the tricarbonylcycloheptatriene chromium(0), complex **1** does not react with alkenes to give [6π + 2π] cycloadducts.[7]

[6 + 2 + 2] Higher-order Cycloaddition Reactions. Rigby and coworkers have advanced the field of multicomponent cycloaddition reactions using thiepin chromium complex **1** and terminal alkynes.[8] The reaction proceeds via a process that can be viewed formally as two consecutive [6π + 2π] cycloaddition events to give tetracycle **5** (eq 2). The cycloaddition events occur in the coordination sphere of the chromium, thus the reaction sets the six new stereogenic centers in tetracycle **5** stereospecifically, and only one diastereomer is observed.[9]

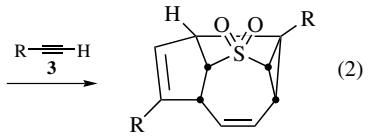
Table 1



Entry	R	R′	Yield
1	Ph	TMS	78%
2	n-Pr	TMS	65%
3	n-Bu	TMS	65%
4	Ph	Et	42%
5	–(CH$_2$)$_6$–		80%



1 **4**

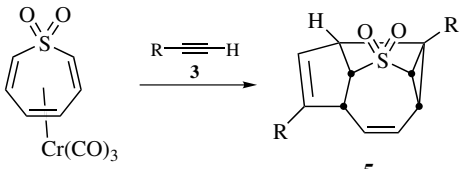


(2)

5

Examples of the [6 + 2 + 2] reaction are included in Table 2.[8a] The reaction requires either photochemical (entries 1–3) or thermal (entry 4) conditions to provide tetracycles **5**.

Table 2

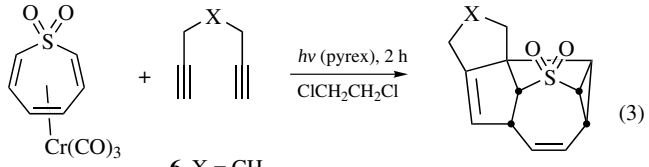


1 **5**

Entry	R	Conditions[a]	Yield
1		A	32
2	t-Bu–	A	70
3	TMS–	B	35
4	TMS–	C	

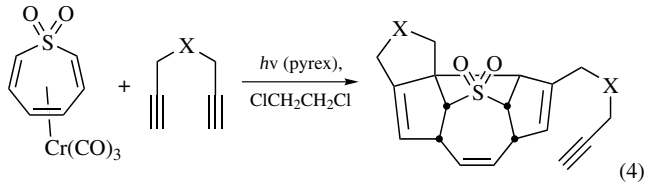
[a] Reaction conditions: (A) hv, U-glass filter, 1,2-dichloroethane, 1 h. (B) hv, pyrex glass filter, 1,2-dichloroethane, 1 h. (C) 160 °C, sealed tube Bu_2O, 12 h.

Furthermore, the 2π components can be tethered together so the new product will have one additional ring. Thus, diyne **6** is slowly added over 2 h to a solution of complex **1** in a photochemical reactor to provide a 57% yield of pentacycle **8**. Likewise, slow addition of diyne **7** gives pentacycle **9** in a diminished yield, presumably due to competitive polymerization (eq 3).[10]



1 **6** X = CH_2; **7** X = $(CH_2)_2$ — *hv* (pyrex), 2 h, $ClCH_2CH_2Cl$ — **8** X = CH_2 57%; **9** X = $(CH_2)_2$ 32% (3)

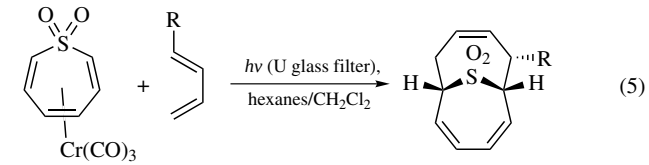
[6 + 2 + 2 + 2] Higher-order Cycloaddition Reactions. Recently, Rigby and coworkers observed another product during their studies on the three component cycloaddition reactions using tethered alkynes. Thus, a photochemically promoted reaction between thiepin chromium complex **1** and excess octa-1,7-diyne **10** gave pentacycle **12** in 45% yield. Likewise, nonadiene **11** provided pentacycle **13** in 38% yield (eq 4).[11]



1 **10** X = $(CH_2)_2$; **11** X = $(CH_2)_3$ — *hv* (pyrex), $ClCH_2CH_2Cl$ — **12** X = $(CH_2)_2$ 45%; **13** X = $(CH_2)_3$ 38% (4)

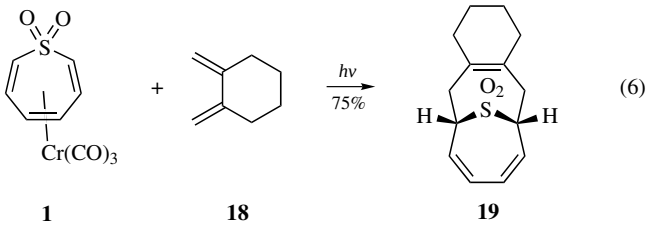
The mechanism leading to pentacycles **12** and **13** has not been established; however, the reaction may proceed via two sequential $[6\pi + 2\pi]$ cycloaddition reactions followed by a what appears to be a [3 + 2] cycloaddition. If the final step involves a [3 + 2] cycloaddition reaction, then these examples would represent the first examples of a chromium-mediated [3 + 2] cycloaddition reaction.[11]

[6 + 4] Higher-order Cycloaddition Reactions. By far, the most extensively investigated reaction of chromium complex **1** is the $[6\cdot + 4\cdot]$ cycloaddition reaction.[4,7a,12] The reaction between complex **1** and several dienes was examined, and it was determined that electron-rich $4\cdot$ partners provided much higher yields than those of electron deficient partners. Thus, diene **14** reacts with chromium complex **1** under photochemical conditions to give an excellent yield of cycloadduct **15**, whereas, diene **16** gives a 38% yield of the corresponding cycloadduct **17** (eq 5).[12b]

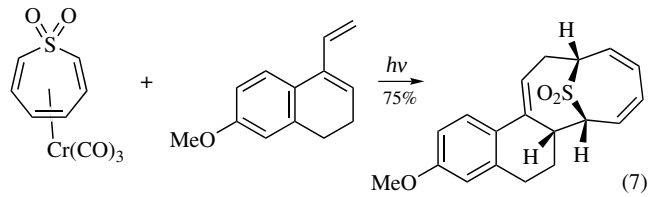


1 **14** R = OAc; **16** R = CO_2Me — *hv* (U glass filter), hexanes/CH_2Cl_2 — **15** R = OAc 78%; **17** R = CO_2Me 38% (5)

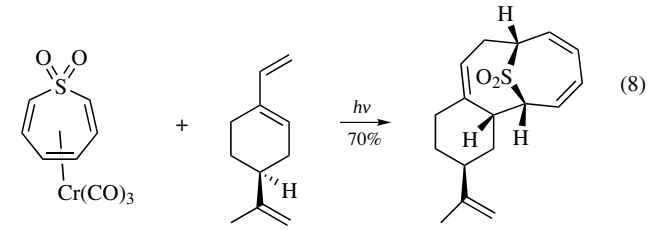
Other more complex dienes have also been examined in this reaction and are listed below (eq 6–9).[7,13]



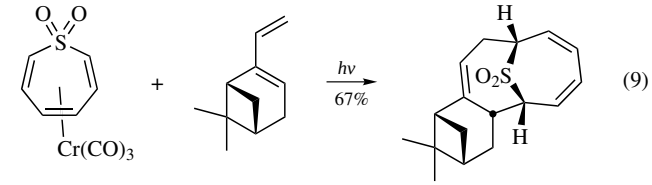
1 **18** — *hv*, 75% — **19** (6)



1 **20** — *hv*, 75% — **21** (7)

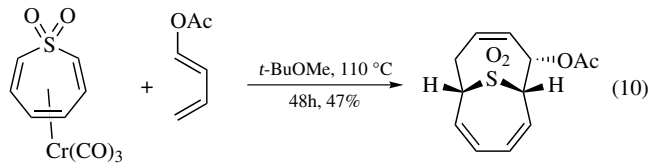


1 **22** — *hv*, 70% — **23** (8)



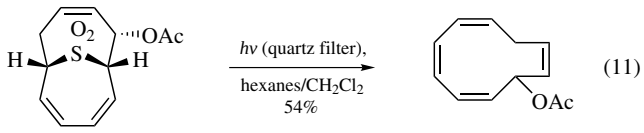
1 **24** — *hv*, 67% — **25** (9)

The $[6\pi + 4\pi]$ cycloaddition reaction can also be promoted thermally. For example, a *tert*-butylmethylether solution of chromium complex **1** and diene **14** was heated to reflux (110 °C) for 48 h. Upon isolation via column chromatography on silica gel, compound **15** was again obtained but with a diminished yield (47%) (eq 10).[12b]



1 **14** — *t*-BuOMe, 110 °C, 48h, 47% — **15** (10)

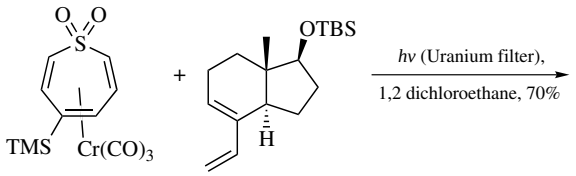
Sulfur Dioxide Extrusion and Applications Toward Total Synthesis. The sulfur-containing products, which result from the higher-order cycloaddition reactions described above, have been submitted to various conditions to extrude the elements of sulfur dioxide. For example, photolysis (quartz filter) of cycloadduct **15** for 15 min promotes a cheletropic extrusion of sulfur dioxide to give a 54% yield of cyclodecatetraene **26** (eq 11).[4]



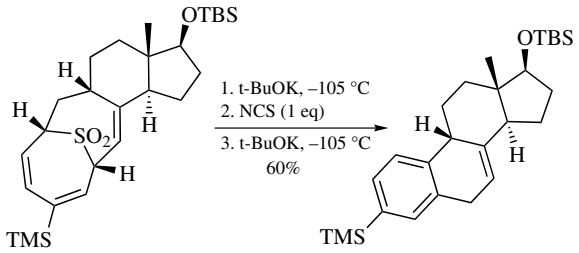
(11)

15 **26**

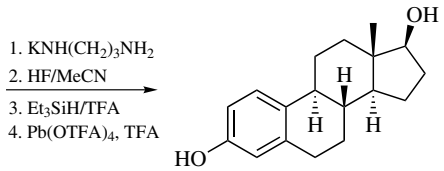
A very different sulfur dioxide extrusion protocol has been applied to the total synthesis of (+)-estradiol (**30**) by Rigby and coworkers.[13] In the event, the trimethylsilyl-substituted chromium thiepin complex **27** participated in a $[6\pi + 4\pi]$ cycloaddition reaction to provide a 70% yield of the structurally complex dihydrothepin **28**. Subsequent sulfur dioxide extrusion via a Ramberg-Bäcklund-type ring contraction gave tetracycle **29**. The total synthesis of (+)-estradiol (**30**) was completed using a four-step sequence of standard reactions (eq 12).[13]



1 **27**



28 **29**



(12)

(+)-estradiol (**30**)

Related Reagents. Tricarbonyl[(2,3,4,5,6,7-η)-cyclo-heptatriene]chromium(0);[1] Tricarbonyl[(2,3,4,5,6,7-η)-thiepin-1,1-dioxide]molybdenum(0);[12b] Tricarbonyl[(2,3,4,5,6,7-η)-thiepin-1,1-dioxide]tungsten(0);[12b] Tricarbonyl[(2,3,4,5,6,7-η)-thiepin]-iron(0);[14] Tricarbonyl[(2,3,4,5,6,7-η)methyl-1*H*-azepine-1-carboxylate]chromium;[4] Thiepin-1,1-dioxide;[2] Trisaceto-nitrile-tricarbonyl-chromium(0).[3]

1. Rigby, J. H.; Fales, K. R., *Org. Syn.* **1999**, *77*, 121.
2. (a) Mock, W. L., *J. Am. Chem. Soc.* **1967**, *89*, 1281. (b) Mock, W. L.; McCausland, J. H., *J. Org. Chem.* **1976**, *41*, 242.
3. Tate, D. P.; Knipple, W. R.; Augl, J. M., *Inorganic Chem.* **1962**, *1*, 433.
4. Rigby, J. H.; Ateeq, H. S.; Krueger, A. C., *Tetrahedron Lett.* **1992**, *33*, 5873.
5. For reviews on higher-order cycloaddition chemistry, see: (a) Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford; 1991, Vol. 5, p 593 (b) Rigby, J. H. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford; 1991, Vol. 5, p 617. (c) Wender, P. A.; Siggel, L.; Nuss, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford; 1991, Vol. 5, p 645.
6. Rigby, J. H.; Warshakoon, N. C., *Tetrahedron Lett.* **1997**, *38*, 2049.
7. (a) Rigby, J. H., *Tetrahedron* **1999**, *55*, 4521. (b) Warshakoon, N. C., Ph.D. *Dissertation*, Wayne State University, 1998.
8. (a) Rigby, J. H.; Warshakoon, N. C.; Heeg, M. J., *J. Am. Chem. Soc.* **1996**, *118*, 6094. (b) For a review on metal promoted cycloaddition reactions, see: Lautens, M.; Klute, W.; Tam, W., *Chem. Rev.* **1996**, *96*, 49.
9. An iron(0)-mediated process between cycloheptatriene and and alkyne resulting in a [6 + 2 + 2]-type product was first reported by: Goddard, R.; Woodward, P., *J. Chem. Soc., Dalton Trans.* **1979**, 711.
10. Rigby, J. H.; Heap Charles, R.; Warshakoon, N. C., *Tetrahedron* **2000**, *56*, 2305.
11. Rigby, J. H.; Heap Charles, R.; Warshakoon, N. C.; Heeg, M. J., *Org. Lett.* **1999**, *1*, 507.
12. (a) Rigby, J. H.; Warshakoon, N. C., *J. Org. Chem.* **1996**, 61, 7644. (b) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J., *J. Am. Chem. Soc.* **1993**, *115*, 1382.
13. Rigby, J. H.; Warshakoon, N. C.; Payen, A. J., *J. Am. Chem. Soc.* **1999**, *121*, 8237.
14. Nishino, K.; Tagagi, M.; Kawata, T.; Murata, I.; Inanaga, J.; Nakasuji, K., *J. Am. Chem. Soc.* **1991**, *113*, 5059.

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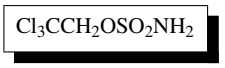
2,2,2-Trichloroethoxysulfonamide



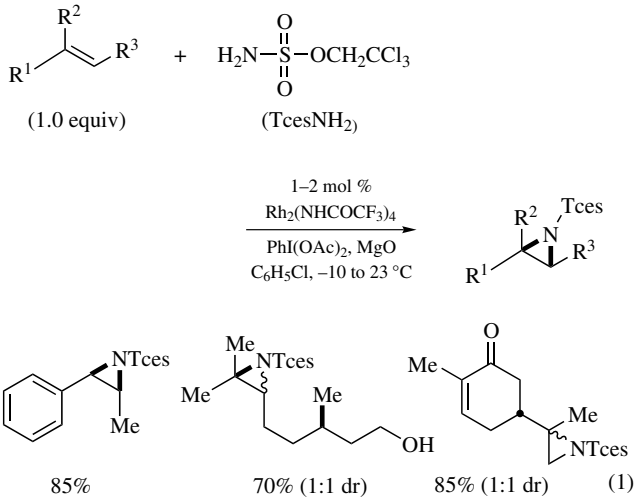
[69226-51-3] $C_2H_4Cl_3NO_3S$ (MW 228.42)
InChI = 1/C2H4Cl3NO3S/c3-2(4,5)1-9-10(6,7)8/h1H2,(H2,6,7,8)/f/h6H2
InChIKey = VOKONKGVTXWZJI-MDVJYLRGCB

(reagent used as a nitrogen source for N-atom transfer reactions (aziridination, C–H insertion); as a starting material for the preparation of imidodithioate derivatives.)

Alternate Names: 2,2,2-trichloroethylsulfamate; sulfamic acid, 2,2,2-trichloroethyl ester.
Physical Data: mp 57–58 °C.
Solubility: sol in alcohol, CH_3CN, THF, EtOAc, CH_2Cl_2, C_6H_6.
Form Supplied in: white solid; commercially available; best prepared from Cl_3CCH_2OH and $ClSO_2NCO$.[1]
Purification: chromatography on silica gel.
Handling, Storage, and Precautions: no special precautions are required, shelf-stable.

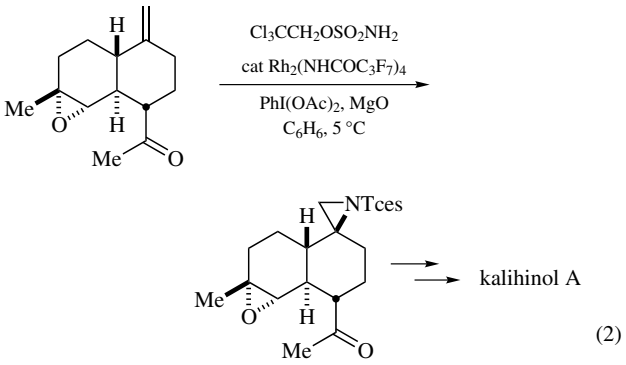
Alkene Aziridination. 2,2,2-Trichloroethoxysulfonamide ($TcesNH_2$) reacts with alkenes in the presence of $PhI(OAc)_2$ and 1–2 mol % of a dirhodium tetraperfluorocarboxamide

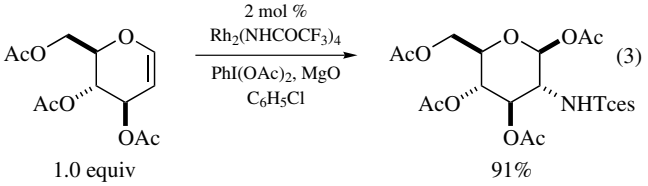
($Rh_2(NHCOR_F)_4$) catalyst to furnish aziridine products (eqs 1 and 2).[2,3] The process uses limiting amounts of the olefin substrate and is effective with both styrenyl and aliphatic derivatives. Reactions are typically performed at 5 °C and proceed in yields ranging from 50 to 90% for most electronically neutral and electronically rich olefins. Reactions with *cis*- and *trans*-substituted alkenes are stereospecific. Allylic amination does not compete with alkene oxidation except in select cases involving reactions with cyclopentene or cyclohexene. The trichloroethoxysulfonyl aziridine (Tces) products are stable to chromatographic purification in most cases, but readily react with nucleophiles to give the ring-opened Tces-amide products. Aziridination of triacetoxyglucal offers efficient access to the amino sugar (eq 3).[2b] In general, the Tces-protecting group can be excised with Zn/AcOH, followed by treatment of the sulfated amine with 1.0 M methanolic HCl to reveal the free amine.



A Cu(I)–*N*-heterocyclic carbene complex, IPrCu(DBM), catalyzes alkene aziridination with $TcesNH_2$, PhI=O, and 4 Å molecular sieves (eq 4).[4] Reactions are performed with limiting alkene; *cis*- and *trans*-disubstituted olefins give isomeric product mixtures. In one example with styrene, $TcesNH_2$, and $PhI(OAc)_2$, 3 mol % of an Au(I) catalyst, [Au(^{t}Bu$_3$tpy)](OTf), is found to catalyze aziridine formation.[5]

***C–H* Amination.** 2,2,2-Trichloroethoxysulfonamide serves as an optimal nitrogen atom source for Rh-catalyzed intermolecular



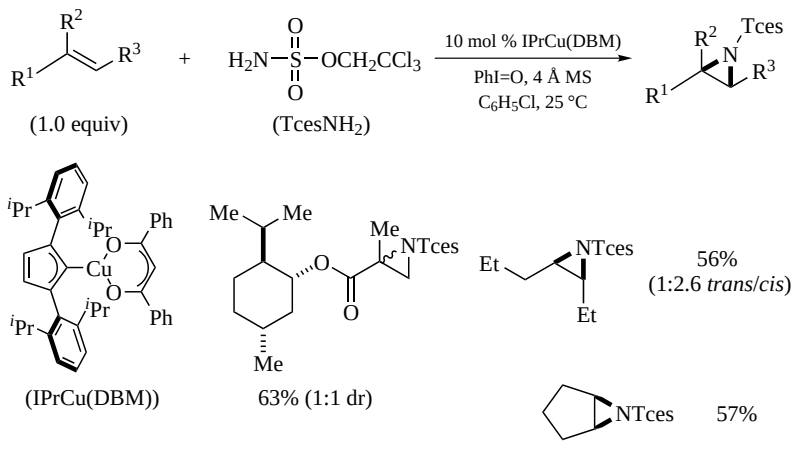


amination of benzylic C–H bonds (eq 5).[1,6] Reactions are performed with limiting amounts of substrate and $PhI(O_2C^tBu)_2$ as the terminal oxidant. Positional selectivity is strongly biased toward benzylic oxidation. Modest yields of 3° C–H amination products can be obtained in select cases. Oxidation of an optically active 3° C–H substrate is stereospecific. Reactions with $Tces^{15}NH_2$ make possible the facile assembly of isotopically labeled compounds (eq 6).

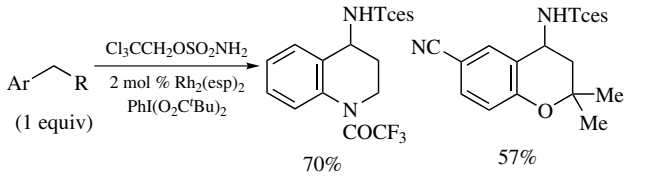
A fluorinated tetraphenylporphyrin–Ru(II) complex, [Ru(F_{20}-TPP)(CO)], reacts with TcesN=IPh to generate a bis-imido Ru(VI) adduct (eq 7).[7] This complex oxidizes benzylic (fluorene, cumene, toluene) and allylic (cyclohexene) hydrocarbons to give the corresponding Tces-amide products. The solid iodoimine oxidant is prepared from $TcesNH_2$, $PhI(OAc)_2$, and KOH.

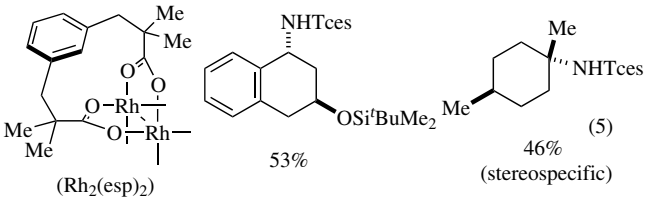
Oxidative Amination of Alkenes. Palladium acetate-catalyzed aerobic oxidation of cyclopentene and cyclooctene using $TcesNH_2$ affords the corresponding allylic amine products (eq 8).[8] Small amounts of isomeric alkene products are also obtained in this reaction.

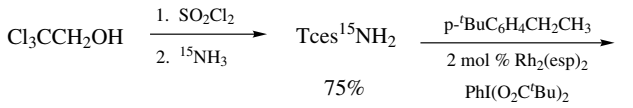
Imidodithioate Synthesis. 2,2,2-Trichloroethoxysulfonamide reacts with CS_2, Me_2SO_4, and NaOH to form the

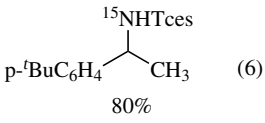


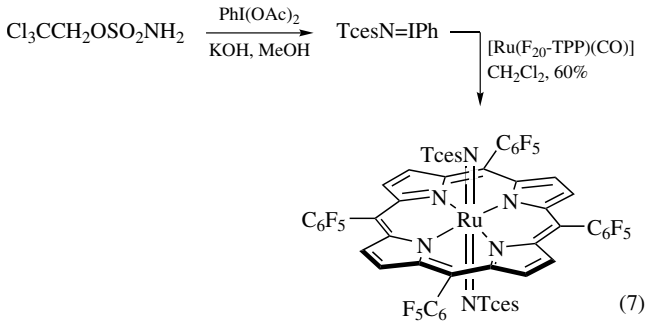
corresponding imidodithioate (eq 9).[9] This reagent functions as a useful precursor for Tces-guanidine synthesis.[10] Reaction of TcesN=C $(SMe)_2$ with NH_3 or SO_2Cl_2 generates the isothiourea or imidochloride, respectively.

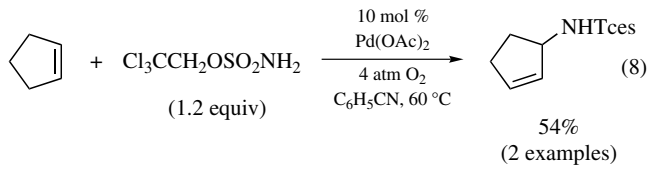


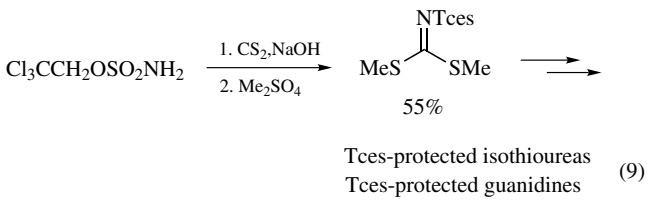




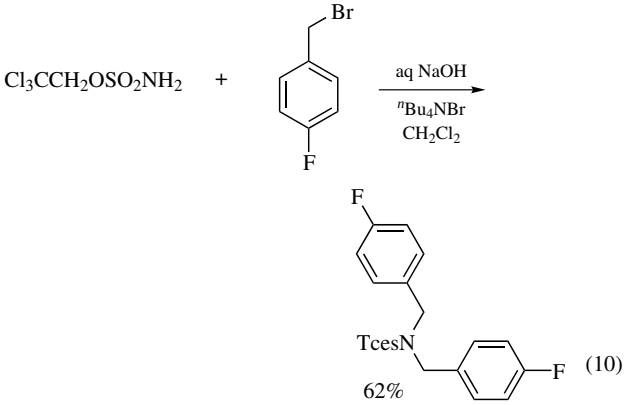








Sulfamate *N*-Alkylation. *N*,*N*-Dialkylation of $TcesNH_2$ occurs smoothly under biphasic conditions ($NaOH–H_2O/CH_2Cl_2$) using $^nBu_4NBr$ as a phase-transfer catalyst (eq 10).[11] $TcesNH_2$ and related sulfamate derivatives have been shown to act as inhibitors of estrone sulfatase.[12]



Related Reagents. *p*-Toluenesulfonamide; *o*-Nitrobenzenesulfonamide; 2-(Trimethylsilyl)ethylsulfonamide.

1. Fiori, K. W.; Du Bois, J., *J. Am. Chem. Soc.* **2007**, *129*, 562.
2. (a) Guthikonda, K.; Du Bois, J., *J. Am. Chem. Soc.* **2002**, *124*, 13672. (b) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J., *Tetrahedron* **2006**, *62*, 11331.
3. Keaney, G. F.; Wood, J. L., *Tetrahedron Lett.* **2005**, *46*, 4031.
4. Xu, Q.; Apella, D. H., *Org. Lett.* **2008**, *10*, 1497.
5. Li, Z.; Ding, X.; He, C., *J. Org. Chem.* **2006**, *71*, 5876.
6. For a closely related, stereoselective C–H amination process, see Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P., *J. Am. Chem. Soc.* **2008**, *130*, 343.
7. Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M., *J. Org. Chem.* **2004**, *69*, 3610.
8. Rogers, M. M.; Kotov, V.; Chatwichien, J.; Stahl, S. S., *Org. Lett.* **2007**, *9*, 4331.
9. Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J., *Org. Lett.* **2006**, *8*, 1073.
10. Mulcahy, J. V.; Du Bois, J., *J. Am. Chem. Soc.* **2008**, *130*.
11. (a) Hedayatullah, M.; Beji, M., *Phosphorus Sulfur* **1988**, *39*, 205. (b) Debbabi, K.; Beji, M.; Baklouti, A., *Phosphorus, Sulfur, and Silicon* **2005**, *180*, 1545.
12. (a) Ahmed, S.; Owen, C. P.; James, K.; Patel, C. K.; Sampson, L., *J. Steroid Biochem. Mol. Biol.* **2002**, *80*, 429. (b) Ahmed, S.; James, K.; Owen, C. P.; Patel, C. K.; Sampson, L., *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1279.

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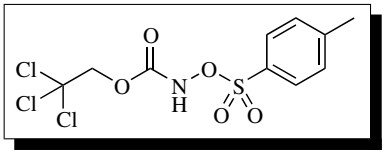
2,2,2-Trichloroethyl-*N*-tosyloxycarbamate



[931109-52-3] $C_{10}H_{10}Cl_3NO_5S$ (MW 362.61)

InChI = 1/C10H10Cl3NO5S/c1-7-2-4-8(5-3-7)20(16,17)19-14-9(15)18-6-10(11,12)13/h2-5H,6H2,1H3,(H,14,15)/f/h14H

InChIKey = XZOGFKHDQLSQJN-YHMJCDSICG

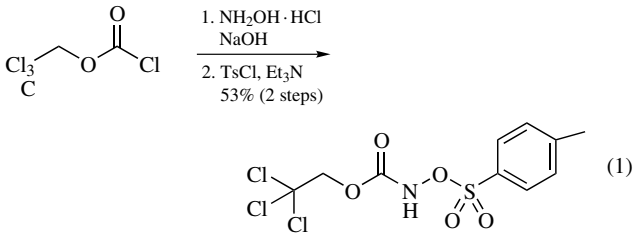
(reagent used as a metal nitrene precursor for C–H insertion and aziridination reactions)

Physical Data: mp 123 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.90 (d, J = 8.43 Hz, 2H), 7.36 (d, J = 8.01 Hz, 2H), 4.65 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.6, 146.5, 130.0, 129.9, 129.7, 94.1, 75.1, 21.8

Solubility: sol aromatic hydrocarbons (toluene, benzene, chlorobenzene), chloroform, dichloromethane, ethyl acetate; slightly soluble ether.

Form Supplied in: white solid.

Preparative Methods: *N*-tosyloxycarbamates are easily prepared from the corresponding chloroformate by treatment with hydroxylamine, followed by a standard tosylation reaction (eq 1).

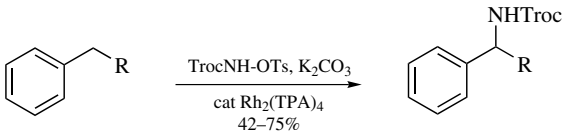


(1)

Purification: recrystallized from a mixture of chloroform/hexanes (1/1) or flash chromatography on silica gel with 1% EtOAc/dichloromethane as eluent.

Handling, Storage, and Precautions: stable at room temperature for up to 6 months; thermogravimetry analysis showed decomposition above 180 °C.

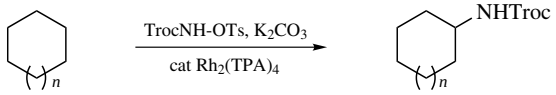
C–H Insertion Reactions. *N*-Tosyloxycarbamates have been developed as alternative metal nitrene precursors to iminoiodinane reagent for performing C–H insertion reactions.[1–3] More specifically, 2,2,2-trichloroethyl-*N*-tosyloxycarbamate has been designed as a reagent to perform intermolecular C–H insertion reactions in the presence of potassium carbonate and a rhodium dimer catalyst.[4] This reagent lacks C–H bonds at the δ-position, thus precluding competitive intramolecular reactions. A similar backbone has been reported for a sulfamate reagent used in intermolecular C–H insertion reaction with diacetoxyiodobenzene.[5] The reaction of 2,2,2-trichloroethyl-*N*-tosyloxycarbamate with aromatic alkanes in the presence of potassium carbonate and 6 mol % of rhodium(II) triphenylacetate dimer ($Rh_2(TPA)_4$) produced the desired trichloroethylcarbamate (Troc)-protected benzylic amine in good yields (eq 2). Not only secondary C–H bonds were reacted, but also primary amines were obtained in good yields. A number of functional groups were tolerated, including methoxy, halogeno, and nitro groups.



(2)

R = H, Me, 4-MeOPh, 4-FPh, 3-NO_2Ph

In the presence of a chiral catalyst such as rhodium(II) (*S*)-*N*-1,8-naphthanoyl-*tert*-leucinate dimer, Troc-amino indane was produced with 56% yield and 2.57:1 enantiomeric ratio. In contrast to other methods, no hypervalent iodine reagent (typically used stoichiometrically or in excess and forming iodobenzene as by-product) is required for oxidation of the amine component. However, a slight excess of the aromatic alkane component (5 equiv) must be used to achieve good conversions. The reactivity of rhodium nitrenes generated from 2,2,2-trichloroethyl-*N*-tosyloxycarbamate with aliphatic alkanes is similar to the one observed with metal nitrenes obtained from the oxidation of sulfamate with hypervalent iodine reagent. Troc-protected amino cyclohexane and cyclooctane were obtained, respectively, in 73 and 62% yields when 2 equiv of alkanes was used, whereas yields up to 85% were observed with 5 equiv (eq 3).

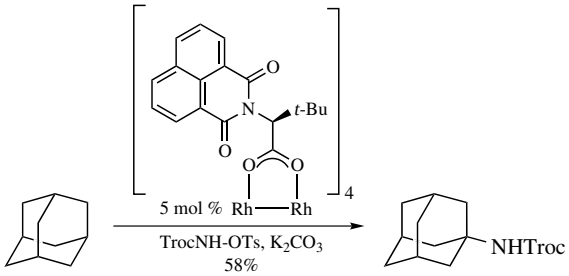


(3)

n = 1, 73% (2 equiv)
85% (5 equiv)

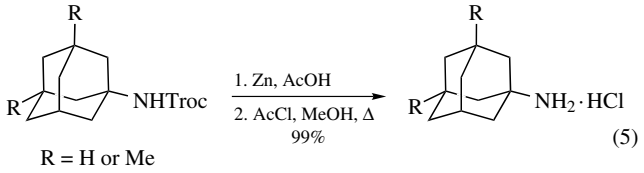
n = 3, 62% (2 equiv)
81% (5 equiv)

With nonsymmetrical substrates, the use of rhodium(II) (*S*)-*N*-1,8-naphthanoyl-*tert*-leucinate dimer as catalyst led to better selectivities in some cases. The corresponding protected aminoadamantane was indeed produced in 58% yield (eq 4).

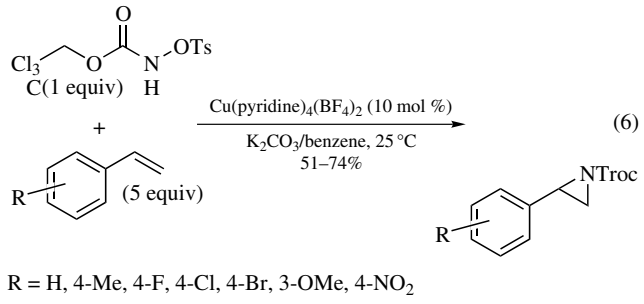


(4)

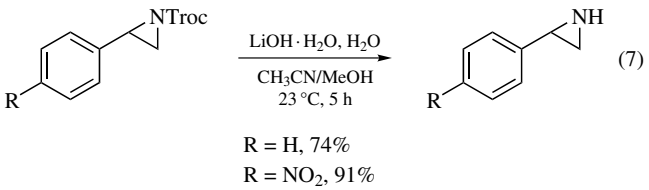
Troc protecting groups are easy to remove, which is an advantage associated with the use of 2,2,2-trichloroethyl-*N*-tosyloxycarbamate as a nitrene precursor compared to arylsulfamate, which require harsh reaction conditions to obtain the free amine. Both amantadine (R = H) and memantine (R = Me) hydrochloride were prepared in quantitative yields from the corresponding Troc-protected amino compounds (eq 5).[6]



Aziridination Reactions. Metal nitrenes are also known to undergo aziridination of alkenes.[7] Copper-catalyzed aziridinations of styrene derivatives have thus been reported using 2,2,2-trichloroethyl-*N*-tosyloxycarbamate as a nitrene precursor (eq 6).[8]



In contrast to other methods, free aziridines can be produced in good yields using mild basic reaction conditions (eq 7).



1. Muller, P.; Fruit, C., *Chem. Rev.* **2003**, *103*, 2905.
2. Davies, H. M. L., *Angew. Chem., Int. Ed.* **2006**, *45*, 6422.
3. Lebel, H.; Huard, K.; Lectard, S., *J. Am. Chem. Soc.* **2005**, *127*, 14198.
4. Lebel, H.; Huard, K., *Org. Lett.* **2007**, *9*, 639.
5. Fiori, K. W.; DuBois, J., *J. Am. Chem. Soc.* **2007**, *129*, 562.
6. Huard, K.; Lebel, H., *Chem. Eur. J.* **2008**, *14*, 6222.
7. Guthikonda, K.; Du Bois, J., *J. Am. Chem. Soc.* **2002**, *124*, 13672.
8. Lebel, H.; Lectard, S.; Parmentier, M., *Org. Lett.* **2007**, *9*, 4797.

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Triethylsilyl Trifluoromethanesulfonate[1]

$Et_3SiOSO_2CF_3$

[79271-56-0] $C_7H_{15}F_3O_3SSi$ (MW 264.38)
InChI = 1/C7H15F3O3SSi/c1-4-15(5-2,6-3)13-14(11,12)7(8,9)10/h4-6H2,1-3H3
InChIKey = STMPXDBGVJZCEX-UHFFFAOYAA

(potent silylating agent;[2–4] Lewis acid catalyst)

Physical Data: 85–86 °C/12 mmHg; *d* 1.169 g cm^{-3}.

Solubility: readily sol hydrocarbons, dialkyl ethers, halogenated solvents. CH_2Cl_2 is employed most commonly. Reactions in 1,2-dichloroethane proceed faster than those in CCl_4 or Et_2O. Protic solvents and THF react with trialkylsilyl triflates and are therefore not suitable.

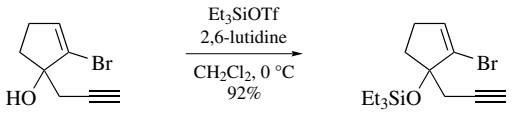
Form Supplied in: neat colorless liquid.

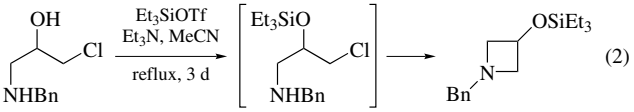
Preparative Methods: can be prepared by reacting chlorotriethylsilane with trifluoromethanesulfonic acid followed by distillation.[1]

Handling, Storage, and Precautions: trialkylsilyl triflates are generally corrosive and moisture sensitive. Appropriate precautions should be taken to ensure that the reagent is handled and stored under rigorously anhydrous conditions.

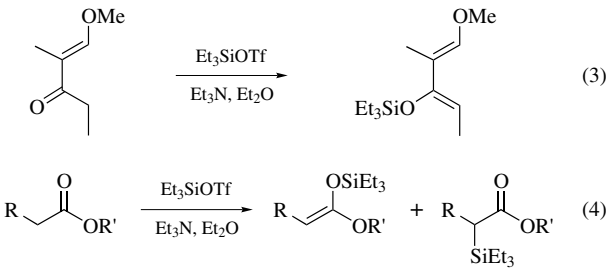
Reactive Silylating Agent. Triethylsilyl ethers are generally more stable towards hydrolysis than are trimethylsilyl ethers, and consequently the Et_3Si moiety has gained increasing use as a protecting group for alcohols. However, since it is often difficult to silylate sterically hindered hydroxyl groups using Et_3SiCl, triethylsilyl perchlorate and triethylsilyl triflate (Et_3SiOTf) were introduced to overcome this problem. Although both reagents are much more potent than Et_3SiCl, the triflate is considered to be safer than the perchlorate and is more convenient because it is commercially available.

Secondary and tertiary alcohols can be silylated under mild conditions using Et_3SiOTf and 2,6-lutidine or a trialkylamine as a proton scavenger (eqs 1 and 2).[2–4]

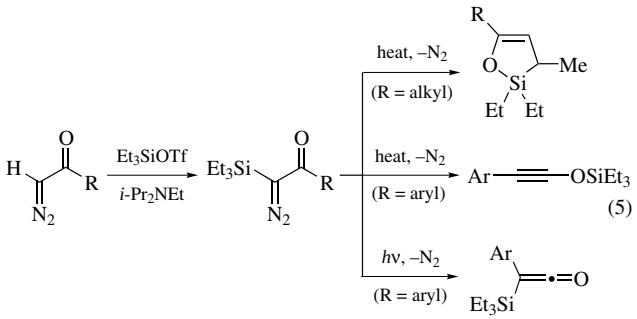




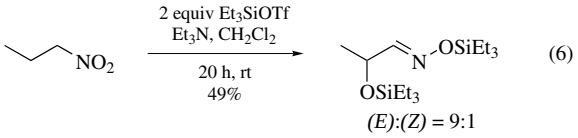
Silyl enol ethers can be conveniently prepared by treatment of ketones with Et_3SiOTf and triethylamine (eq 3).[1,5] Similarly, esters can be converted to silyl ketene acetals; however, large amounts of the *C*-silylated product may also be isolated (eq 4).[1,6,7] Equilibration of *O*- and *C*-silylated products may occur in the presence of catalytic amounts of Et_3SiOTf.[1]



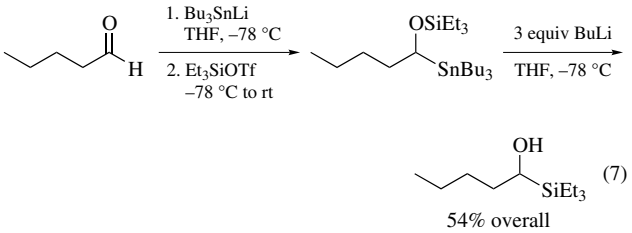
α-Diazo esters react with Et_3SiOTf and Hünig's base (diisopropylethylamine) to give exclusively α-silyl-α-diazo esters, which can be converted to other silylated compounds by loss of dinitrogen (eq 5).[8]



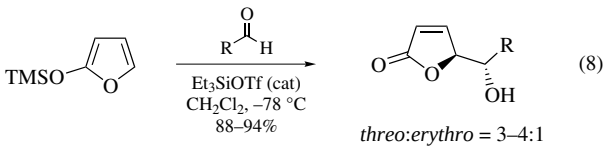
Nitroalkanes have been shown to give α-siloxy *O*-silyloximes upon reaction with two molar equivalents of the silylating agent (eq 6).[9] The reaction is believed to proceed via a nitrogen-to-carbon 1,3-silyloxy rearrangement.



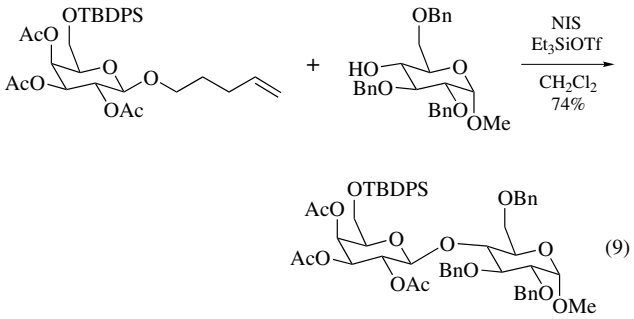
Linderman and Ghannam have utilized Et_3SiOTf to trap the alkoxide formed from the addition of stannyl anion to aldehydes (eq 7).[10] Upon treatment with excess butyllithium, these adducts undergo a reverse Brook rearrangement to afford α-hydroxysilanes.



Lewis Acid Catalyst. Jefford has reported that condensation reactions of 2-trimethylsiloxyfuran with aldehydes can be catalyzed by Et_3SiOTf to give mainly the *threo* addition product (eq 8).[11] Conversely, the *erythro* adduct is favored when fluoride ion is used as the catalyst.



Fraser-Reid has reported that an equimolar mixture of *N*-iodosuccinimide and Et_3SiOTf efficiently promotes the glycosylation of hindered glycoside donors with *n*-pentenyl glycoside acceptors (eq 9).[12]



Related Reagents. Chlorotriethylsilane; Triethylsilyl Perchlorate; Trimethylsilyl Trifluoromethanesulfonate.

1. Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G., *Synthesis* **1982**, 1.
2. Fujiwara, K.; Sakai, H.; Hirama, M., *J. Org. Chem.* **1991**, *56*, 1688.
3. Higgins, R. H., *J. Heterocycl. Chem.* **1987**, *24*, 1489.
4. McCarthy, P. A.; Kageyama, M., *J. Org. Chem.* **1987**, *52*, 4681.
5. Danishefsky, S.; Harvey, D. F., *J. Am. Chem. Soc.* **1985**, *107*, 6647.
6. Emde, H.; Götz, A.; Hofmann, K.; Simchen, G., *Justus Liebigs Ann. Chem.* **1981**, 1643.
7. Emde, H.; Simchen, G., *Justus Liebigs Ann. Chem.* **1983**, 816.
8. (a) Maas, G.; Brückmann, R., *J. Org. Chem.* **1985**, *50*, 2801; (b) Brückmann, R.; Maas, G., *Chem. Ber.* **1987**, *120*, 635.
9. (a) Ferger, H.; Simchen, G., *Justus Liebigs Ann. Chem.* **1986**, 428; (b) Feger, H.; Simchen, G., *Synthesis* **1981**, 378.
10. (a) Linderman, R. J.; Ghannam, A., *J. Am. Chem. Soc.* **1990**, *112*, 2392; (b) Linderman, R. J.; Ghannam, A., *J. Org. Chem.* **1988**, *53*, 2878.
11. Jefford, C. W.; Jaggi, D.; Boukouvalas, J., *Tetrahedron Lett.* **1987**, *28*, 4037.
12. Konradsson, P.; Udodong, U. E.; Fraser-Reid, B., *Tetrahedron Lett.* **1990**, *31*, 4313.

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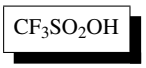
Trifluoromethanesulfonic Acid[1]



[1493-13-6] CHF_3O_3S (MW 150.09)
InChI = 1/CHF3O3S/c2-1(3,4)8(5,6)7/h(H,5,6,7)/f/h5H
InChIKey = ITMCEJHCFYSIIV-JSWHHWTPCD

(one of the strongest organic acids; catalyst for oligomerization/polymerization of alkenes and ethers; precursor for triflic anhydride and several metal triflates; acid catalyst in various reactions)

Alternate Name: triflic acid.
Physical Data: bp 162 °C/760 mmHg, 84 °C/43 mmHg, 54 °C/8 mmHg; *d* 1.696 g cm^{-3}.
Solubility: sol water and in many polar organic solvents such as DMF, sulfolane, DMSO, dimethyl sulfone, acetonitrile; sol alcohols, ketones, ethers, and esters, but these generally are not suitable inert solvents (see below).
Analysis of Reagent Purity: IR;[2] ^{19}F NMR.[3]

Preparative Methods: best prepared by basic hydrolysis of CF_3SO_2F followed by acidification.[2]

Purification: distilled with a small amount of Tf_2O.[4]

Handling, Storage, and Precautions: is a stable, hygroscopic liquid which fumes copiously on exposure to moist air. Transfer under dry nitrogen is recommended. Contact with cork, rubber, and plasticized materials will cause rapid discoloration of the acid and deterioration of the materials. Samples are best stored in sealed glass ampules or glass bottles with Kel-F™ or PTFE plastic screw cap linings. Use in a fume hood.

Original Commentary

Lakshminarayanapuram R. Subramanian, Antonio García Martínez & Michael Hanack
Universität Tübingen, Tübingen, Germany

Reaction with P_2O_5. Trifluoromethanesulfonic acid (TfOH) reacts with an excess of phosphorus(V) oxide to give trifluoromethanesulfonic anhydride (eq 1),[5] while treatment with a smaller amount of P_2O_5 (TfOH:P_2O_5 = 6:1) and slower distillation leads to trifluoromethyl triflate (eq 2).[6]

$$CF_3SO_3H + P_2O_5 \text{ (excess)} \xrightarrow[-H_2O]{\Delta} (CF_3SO_2)_2O \quad (1)$$

$$6\,CF_3SO_3H + P_2O_5 \xrightarrow[70\%]{\Delta} 3\,CF_3SO_2OCF_3 + 3\,SO_2 + 2\,H_3PO_4 \quad (2)$$

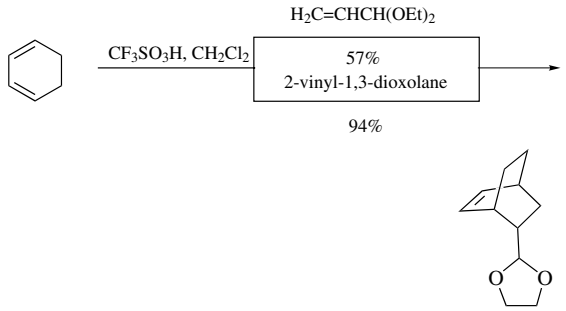
The synthetic utility of trifluoromethyl triflate as a trifluoromethanesulfonylating agent is severely limited, because the reagent is rapidly destroyed by a fluoride-ion chain reaction in the presence of other nucleophiles.[7]

Dehydration of a 2:1 mixture of CF_3CO_2H and TfOH with P_2O_5 affords trifluoroacetyl triflate (eq 3),[8] which is a very reactive agent for trifluoroacetylations at O, N, C, or halogen centers (eq 3).[8a]

$$CF_3SO_3H \xrightarrow[P_2O_5,\ \Delta\ 75\%]{CF_3CO_2H} CF_3CO_2OSO_2CF_3 \xrightarrow[-MeOTf\ 86\%]{\text{anisole, 65 °C, 28 h}} \text{PhOCOCF}_3 \quad (3)$$

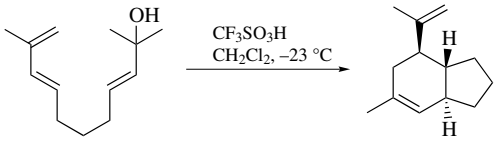
Protonation and Related Reactions. TfOH is one of the strongest monoprotic organic acids known. The acid, and its conjugate base ($CF_3SO_3^-$), have extreme thermal stability, are resistant to oxidation and reduction, and are not a source of fluoride ions, even in the presence of strong nucleophiles. They do not lead to sulfonation as do sulfuric acid, fluorosulfuric acid, and chlorosulfonic acid in some reactions. TfOH is therefore effectively employed in protonation reactions.

The strong protonating property of TfOH is used to generate allyl cations from suitable precursors in low-temperature ionic Diels–Alder reactions. 3,3-Diethoxypropene and 2-vinyl-1,3-dioxolane add to cyclohexa-1,3-diene in the presence of TfOH to give the corresponding Diels–Alder adducts, the latter in high yield (eq 4).[9]



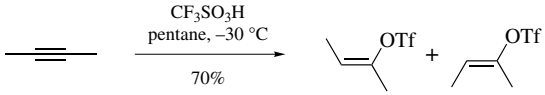
(4)

An intramolecular Diels–Alder reaction with high stereoselectivity occurs involving allyl cations by protonation of allyl alcohols (eq 5).[10]

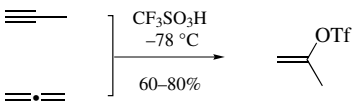


(5)

Alkynes and allenes are protonated with TfOH to give vinyl triflates (eqs 6 and 7),[11] which are precursors to vinyl cations.

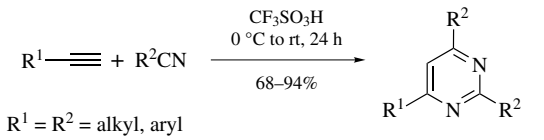


(6)



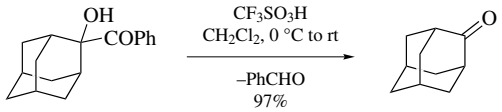
(7)

A convenient synthesis of pyrimidines is developed by protonation of alkynes with TfOH in the presence of nitriles (eq 8).[12]



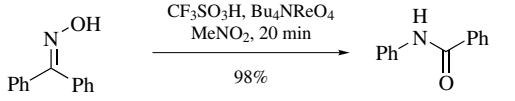
(8)

Triflic acid catalyzes the transformation of α-hydroxy carbonyl compounds to ketones (eq 9).[13]



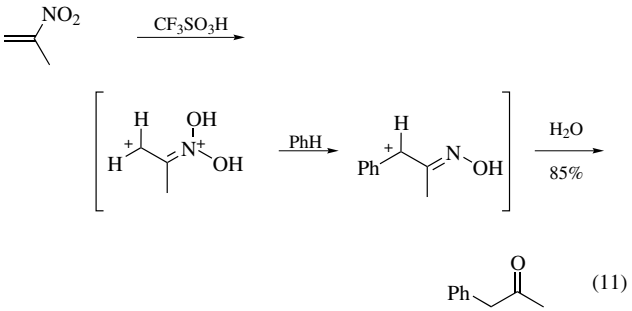
(9)

Oximes undergo Beckmann rearrangement with TfOH in the presence of Bu_4NReO_4 to give amides in high yield (eq 10).[14]



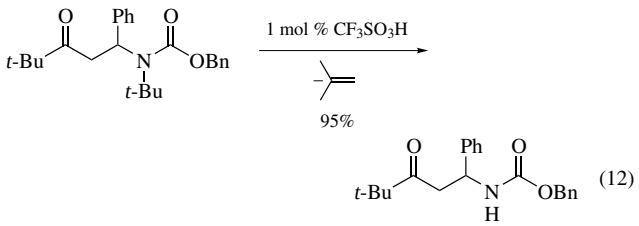
(10)

TfOH protonates nitroalkenes, even nitroethylene, to give *N,N*-dihydroxyiminium carbenium ions, which react with arenes to give arylated oximes. This overall process provides a route to α-aryl methyl ketones from 2-nitropropene (eq 11)[15] and constitutes a versatile synthetic method for the preparation of α-arylated ketones, otherwise difficult to synthesize by the conventional Friedel–Crafts reaction.



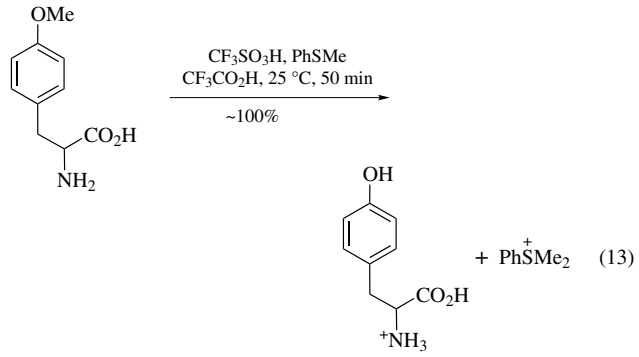
(11)

TfOH catalyzes the removal of *N*-*t*-butyl groups from *N*-substituted *N*-*t*-butylcarbamates to give carbamate-protected primary amines (eq 12).[16]



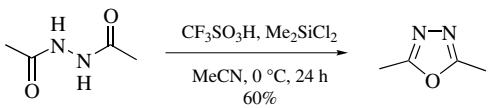
(12)

The methyl group attached to the phenolic oxygen of tyrosine is smoothly cleaved by TfOH in the presence of thioanisole (eq 13).[17] This deblocking method was successfully applied to the synthesis of a new potent enkephalin derivative.



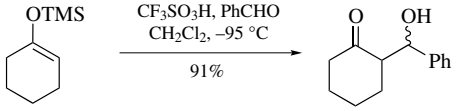
(13)

1,3,4-Oxadiazoles are prepared in good yields from silylated diacylhydrazines (formed in situ) by acid-catalyzed cyclization using TfOH (eq 14).[18]



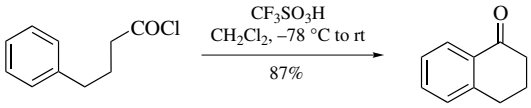
(14)

TfOH protonates naphthalene at room temperature to give a complex mixture of products.[19] TfOH promotes aldol reaction of silyl enol ethers with aldehydes and acetals, leading to new C–C bond formation (eq 15).[20] TfOH competes well with other reagents employed for the aldol reaction, while methanesulfonic acid does not afford any product.



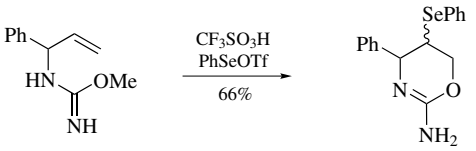
(15)

Cyclization of 3- and 4-arylalkanoic acids to bicyclic ketones is effected by TfOH via the corresponding acid chlorides (eq 16).[21]



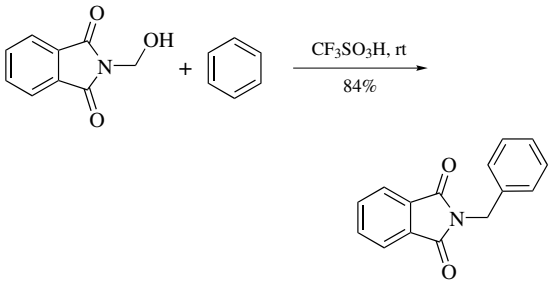
(16)

Allylic *O*-methylisoureas are cyclized with TfOH containing benzeneselenenyl trifluoromethanesulfonate to 5,6-dihydro-1,3-oxazines (eq 17).[22]



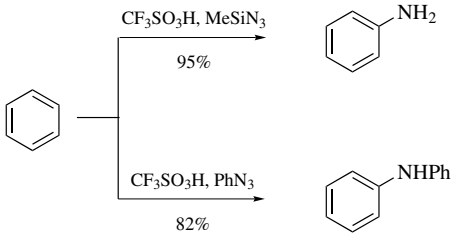
(17)

Tscherniac amidomethylation of aromatics with *N*-hydroxymethylphthalimide in TfOH proceeds smoothly at room temperature to give the corresponding α-amido-methylated products (eq 18).[23]



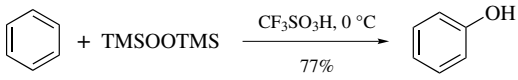
(18)

TfOH catalyzes the amination[24] and phenylamination[25] of aromatics via the corresponding aminodiazonium ion generated from azidotrimethylsilane and phenyl azide respectively (eq 19).



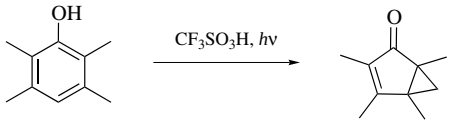
(19)

Electrophilic hydroxylation of aromatics is carried out by protonation of bis(trimethylsilyl) peroxide with TfOH in the presence of the substrate (eq 20).[26]



(20)

Phenol and 2,3,5,6-tetramethylphenol are protonated with TfOH under irradiation to afford rearranged products (eqs 21 and 22).[27]



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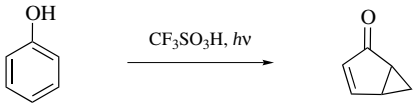
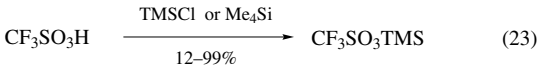


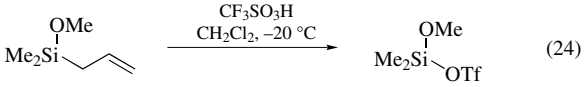
(22)

Other Applications. TfOH is the starting material for the preparation of the electrophilic reagent trimethylsilyl trifluoromethanesulfonate. The latter is prepared by reacting TfOH with chlorotrimethylsilane[28] or more conveniently with Me_4Si (eq 23).[29]



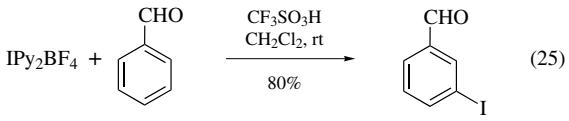
(23)

Functionalized silyl triflates can also be prepared using TfOH (eq 24).[30]



(24)

Reaction of aromatic compounds with bis(pyridine) iodonium(I) tetrafluoroborate in the presence of TfOH is an effective method to form the monoiodo compounds regioselectively (eq 25).[31]



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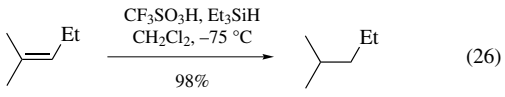
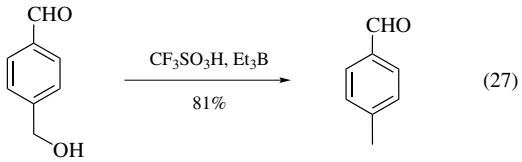
Ionic hydrogenation of alkenes with trialkylsilanes is possible in the presence of the strong acid TfOH, even at −75 °C (eq 26).[32]



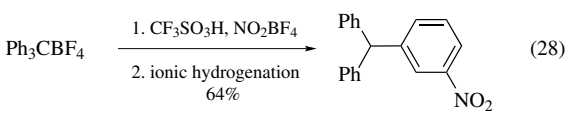
(26)

Hydroxycarbonyl compounds can be selectively reduced to carbonyl compounds by means of TfOH in the presence of trialkylboranes (eq 27).[33]



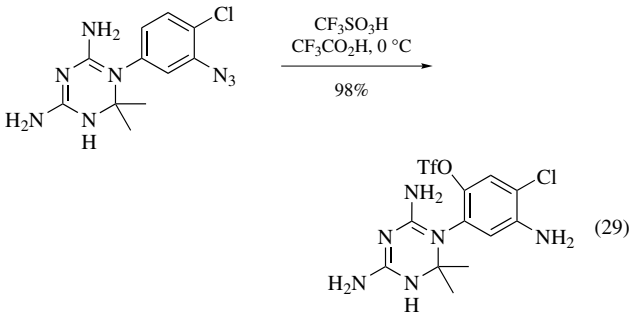
(27)

The triphenylmethyl cation is nitrated with nitronium tetrafluoroborate in the presence of TfOH (eq 28).[34]



(28)

Sterically hindered azidophenyltriazines decompose in TfOH at 0 °C to give isomeric triflates (eq 29).[35]



(29)

Benzoyl triflate prepared from TfOH and benzoyl chloride is a mild and effective benzoylating agent for sterically hindered alcohols[36] and acylative ring expansion reactions.[37] The applications of TfOH in Koch–Haaf carboxylation,[38] Fries rearrangement,[39] and sequential chain extension in carbohydrates[40] are also documented. Recent applications of TfOH in cyclization reactions have been published.[41–43]

First Update

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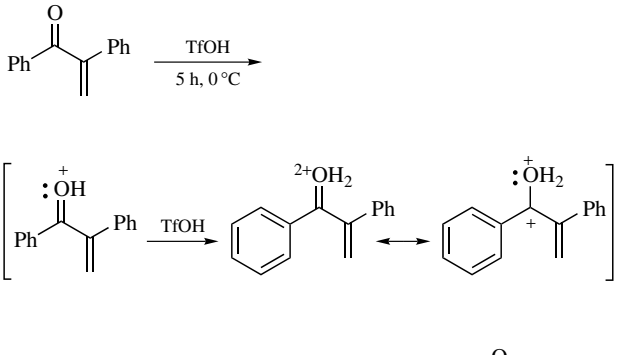
Superelectrophilic Activation or Superelectrophilic Solvation. Trifluoromethanesulfonic acid (triflic acid, TfOH) has been extensively employed as a superacid ($H_o = -14.1$) in superelectrophilic activation (or superelectrophilic solvation), both concepts advanced by Olah.[44,45] Superelectrophilic activations may occur when a cationic electrophile reacts with a Bronsted or Lewis acid to give a dicationic (doubly electron-deficient) superelectrophile. However, it should be recognized that the activation may proceed through superelectrophilic solvation without necessarily forming limiting dicationic intermediates. The frequently used depiction of protosolvated species as their limiting dications is just for simplicity.[45]

Carboxonium ions are highly stabilized by strong oxygen participation and therefore are much less reactive compared to alkyl cations. However, under the superelectrophilic solvation by triflic acid, the Friedel–Crafts-type reactions still can occur via a protosolvated reactive intermediate. For example, 1-phenyl-2-propen-1-ones can be readily transformed into 1-indanones in good yields through triflic acid-catalyzed reaction (eq 30).[46]

A one-pot synthesis of 1-indanones and 1-tetralones in good to excellent yields have been developed by reacting a series of alkenyl carboxylic acid derivatives with arenes in TfOH medium. The reaction involves dicationic intermediates involving intermolecular alkylation followed by intramolecular acylation (eq 31).[47] These reactions have been further investigated.[48]

Dicarboxylic acids can also form a variety of distonic superelectrophilic intermediates by TfOH-mediated protonation of the carboxylic acid group and ionization of adjacent functional groups.

α-Keto dicarboxylic acids in strongly acidic medium generate reactive multiply charged electrophilic species capable of condensing with arenes in high yields (eq 32).[49] The cascade of reactions also involve the loss of carbon monoxide.



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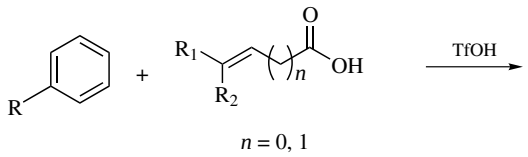

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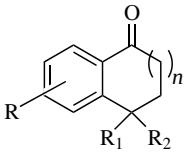
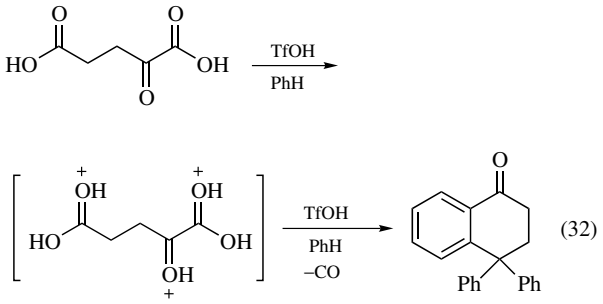


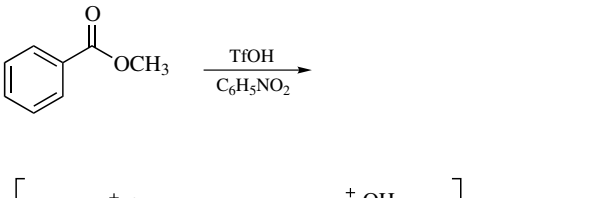


(32)

89%

Triflic acid-catalyzed Friedel–Crafts acylation reactions of aromatics with methyl benzoate give benzophenone products in good to excellent yields (eq 33).[50] To explain the high level of electrophilic reactivity of this system, protosolvated species are proposed as possible intermediates (eq 32). In the triflic acid-catalyzed cyclization of some ethylene dications, protonation of the ester group is thought to be a key activation step. Reaction of α-(methoxycarbonyl)diphenylmethanol with TfOH gives the fluorene product in 94% yield (eq 34).[51]

The same concept was applied in the synthesis of aryl-substituted piperidines by the TfOH-catalyzed reaction of piperidones with benzene (eq 35).[52] In the TfOH-catalyzed reactions, acetyl-substituted heteroaromatic compounds, such as pyridines, thiazoles, quinolines, and pyrazines can condense with benzene in good yields via the dicationic intermediates (eq 36).[53] Amino alcohols have also been found to ionize cleanly to the dicationic intermediates, which were directly observed by low-temperature ^{13}C NMR.[54] Amino alcohols can react with benzene in triflic acid by electrophilic aromatic substitution with 70∼99% yields (eq 37).[54] Similarly, amino acetals can react with benzene in triflic acid medium to give 1-(3,3-diphenylpropyl)amines or 1-(2,2-diphenylethyl)amines in 50∼99% yield (eq 38).[55]



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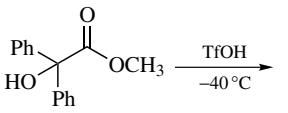
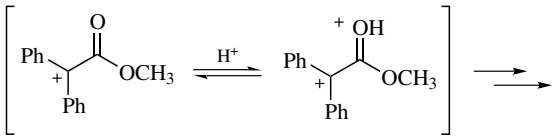
82%





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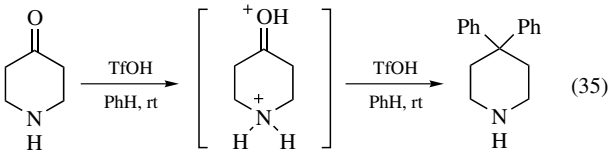
94%



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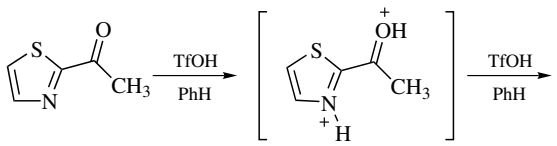
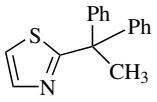
99%





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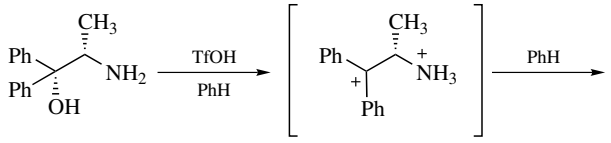
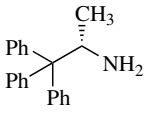
75%





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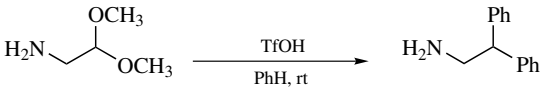
80%

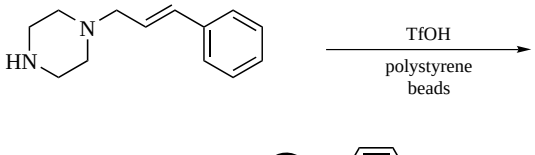


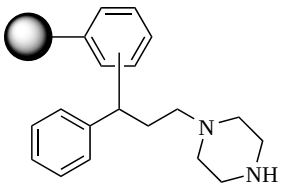
(38)

95%

Klumpp and co-workers reported the triflic acid-catalyzed reactions of olefinic amines with benzene to give addition products in 75∼99% yields.[56] Remarkably, the chemistry was also used to conveniently prepare functionalized polystyrene beads having pendant amine groups (eq 39).[56] In the triflic acid medium, amides are also able to form reactive, dicationic electrophiles.[57] It has been shown that protonated amide increases the reactivity of an adjacent electrophilic group (eq 40), and the protonated amide itself shows enhanced reactivity for Friedel-Crafts acylation arising from an adjacent cationic charge (eq 41).[57] Similar types of TfOH-catalyzed Friedel-Crafts acylation of aromatics with β-lactams have been reported.[58] TfOH-mediated activation of α,β-unsaturated amides for condensation with arenes have been disclosed by Koltunov co-workers.[59] Klumpp and co-workers have also demonstrated the triflic acid-catalyzed superelectrophilic reactions of 2-oxazolines with benzene to give the corresponding amide products.[60] When aminoalkynes and related heterocycles reacted with benzene in triflic acid, diarylated products were obtained in generally good yields (69∼99%) via dicationic intermediates.[61] Triflic acid also promotes reactions of pyrazolecarboxaldehydes with arenes.[62]

In TfOH medium, vinylpyrazine undergoes anti-Markownikow addition involving superelectrophilic intermediates. Arylation of such an electrophile with benzene gave 2-phenylethylpyrazine in high yield (eq 42).[63]





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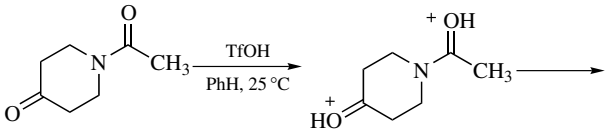
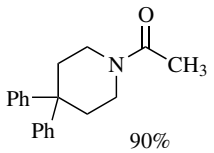
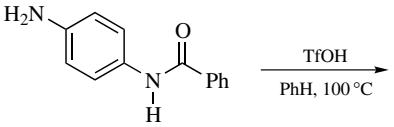
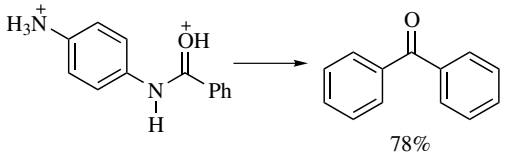




(40)

90%





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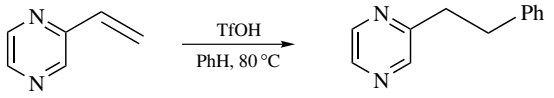
78%

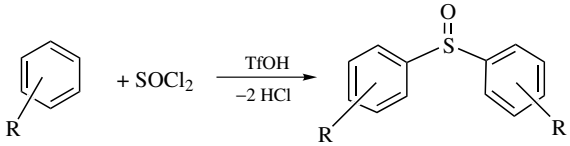


(42)

96%

Ethyl trifluoropyruvate has been activated in TfOH medium for the hydroxyalkylation of arenes to give valuable Mosher's acid derivatives in good to excellent yields.[64] Even Selectfluor® has been activated in TfOH to effect electrophilic fluorination of arenes including fluorobenzene and chlorobenzene.[65]

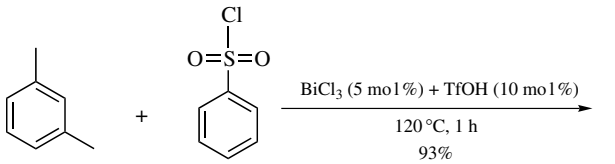
A novel, mild method for the preparation of diaryl sulfoxides from arenes and thionyl chloride has been developed in TfOH medium. Under the nonoxidative reaction conditions only sulfoxides are produced without any contamination from the corresponding sulfones (eq 43).[66]

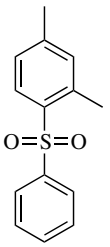


(43)

Other Protonation and Acid-catalyzed Reactions. The catalytic activity of triflic acid can be dramatically increased by the addition of a catalytic amount of bismuth(III) chloride. For

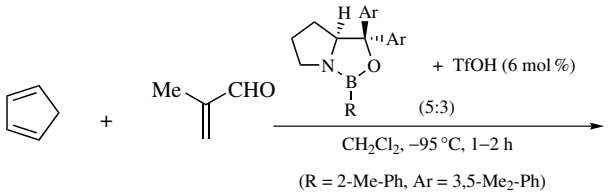
example, triflic acid or $BiCl_3$ by itself poorly catalyzes the sulfonylation of arenes using arenesulfonyl chlorides. However, the $BiCl_3$-triflic acid combination catalysts can efficiently catalyze the sulfonylation reactions (eq 44).[67] Similar synergistic effects between TfOH and bismuth(III) or antimony(III) chlorides have been observed in methanesulfonylation of arenes.[68]

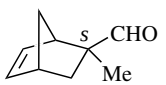




(44)

Corey et al. have shown the asymmetric Diels-Alder reactions catalyzed by a triflic acid activated chiral oxazaborolidine (eq 45).[69] Triflic acid has also been found to be an efficient catalyst (1 mol %) for the hetero-Diels–Alder reaction between aromatic aldehydes and unactivated dienes.[70]

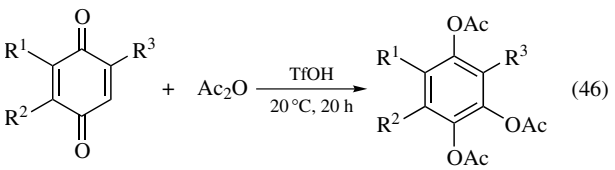




(45)

99% yield, ee = 96%
(*exo*:*endo* = 89:11)

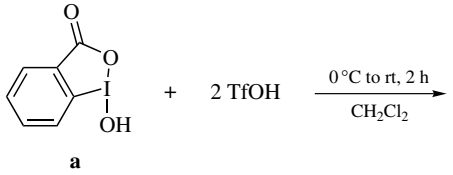
The synthetic scope of the Thiele-Winter reaction of quinines with acetic anhydride can be increased by the use of triflic acid (eq 46).[71] Reaction of cyclopropylacylsilanes with triflic acid in aprotic solvent affords the corresponding cyclobutanone or 2-silyl-4,5-dihydrofuran derivatives.[72] Triflic acid can react with *o*-iodosylbenzoic acid to form a hypervalent iodine reagent, which reacts with 1-trimethylsilylalkynes to afford alkynyliodonium triflates bearing a carboxy group in high yields (eq 47).[73] Reaction of (diacetoxyiodo)benzene [$PhI(OAc)_2$] with excess triflic acid results in oligomerization of $PhI(OAc)_2$.[74]

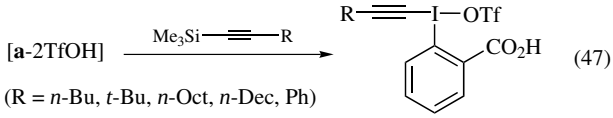


(46)

(R = H, CH_3, Br, OEt, etc.)

92–42%

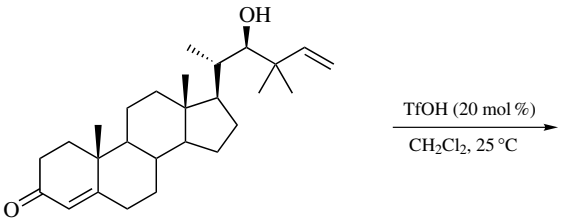


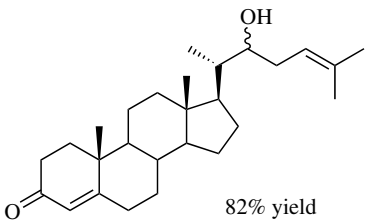


(47)

Olah et al. reported the triflic acid-catalyzed isobutene-isobutylene alkylation, modified with trifluoroacetic acid (TFA) or water. They found that the best alkylation conditions were at an acid strength of about $H_o = -10.7$, giving a calculated research octane number (RON) of 89.1 (TfOH/TFA) and 91.3 (TfOH/H_2O).[75] Triflic acid-modified zeolites can be used for the gas phase synthesis of methyl *tert*-butyl ether (MTBE), and the mechanism of activity enhancement by triflic acid modification appears to be related to the formation of extra-lattice Al rather than the direct presence of triflic acid.[76] A thermally stable solid catalyst prepared from amorphous silica gel and triflic acid has also been reported.[77,78] The obtained material was found to be an active catalyst in the alkylation of isobutylene with *n*-butenes to yield high-octane gasoline components.[77] A similar study has been carried out with triflic acid-functionalized mesoporous Zr-TMS catalysts.[79,80] Triflic acid-catalyzed carbonylation,[81] direct coupling reactions,[82] and formylation[83] of toluene have also been reported. Triflic acid also promotes transalkylation[84] and adamantylation of arenes in ionic liquids.[85] Triflic acid-mediated reactions of methylenecyclopropanes with nitriles have also been investigated to provide [3 + 2] cycloaddition products as well as Ritter products.[86] Triflic acid also catalyzes cyclization of unsaturated alcohols to cyclic ethers.[87]

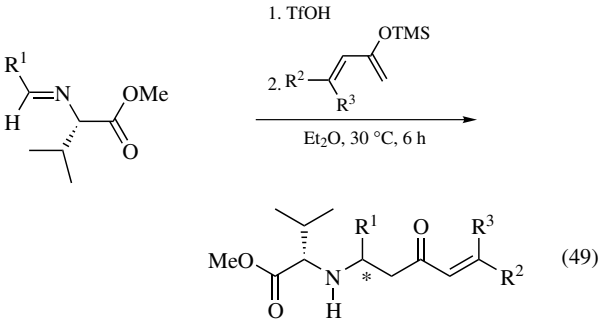
Loh et al. found a triflic acid-catalyzed 2-oxonia Cope rearrangement, which was used in the stereocontrolled synthesis of linear 22*R*-homoallylic sterols (eq 48).[88] Interestingly, poor stereoselectivity was observed when $In(OTf)_3$ was employed as the catalyst for this reaction. Stereoselective Mannich-type reaction of chiral aldimines with 2-silyloxybutadienes in the presence of triflic acid gives the corresponding products with 70–92% de in 62–74% chemical yield, which are not obtained by general Lewis acid-promoted methods (eq 49).[89]





(48)

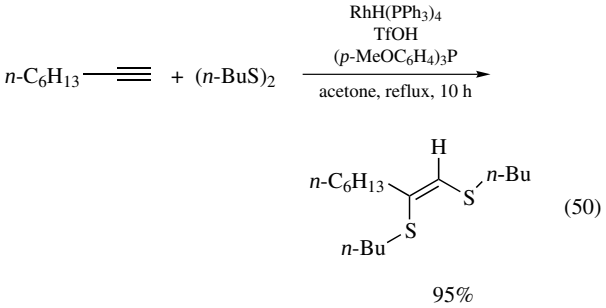
82% yield
22*R*/22*S* = 98:2



(49)

R^1 = Tol, R^2 = Ph, R^3 = H 70% yield, 90% de

Triflic acid was also used in the synthesis of dixanthones and poly(dixanthones) by cyclization of 2-aryloxylbenzonitriles at room temperature.[90] Addition of dialkyl disulfides to terminal alkynes is catalyzed by a rhodium-phosphine complex and triflic acid giving (*Z*)-bis(alkylthio)olefins stereoselectively (eq 50).[91]



(50)

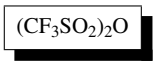
95%

Marko and co-workers have reported the role of triflic acid in the metal triflate-catalyzed acylation of alcohols with carboxylic anhydrides.[92] Their mechanistic insights demonstrate that triflic acid is generated under the acylation reaction conditions, and that two competing catalytic cycles are operating at the same time: a rapid one involving triflic acid and a slower one involving the metal triflates. A straightforward synthesis of aziridines is reported by treating electron rich alkyl- or aryl azide with electron deficient olefin and TfOH in cold acetonitrile.[93]

1. (a) Howells, R. D.; McCown, J. D., *Chem. Rev.* **1977**, *77*, 69. (b) Stang, P. J.; White, M. R., *Aldrichim. Acta* **1983**, *16*, 15.
2. (a) Haszeldine, R. N.; Kidd, J. M., *J. Chem. Soc.* **1954**, 4228. (b) Burdon, J.; Farazmand, I.; Stacey, M.; Tatlow, J. C., *J. Chem. Soc.* **1957**, 2574.
3. Matjaszewski, K.; Sigwalt, P., *Monatsh. Chem.* **1986**, *187*, 2299 (*Chem. Abstr.* **1987**, *106*, 5495).
4. (a) Sagl, D.; Martin, J. C., *J. Am. Chem. Soc.* **1988**, *110*, 5827. (b) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K., *Chem. Pharm. Bull.* **1991**, *39*, 2718.
5. Stang, P. J.; Hanack, M.; Subramanian, L. R., *Synthesis* **1982**, 85.
6. Hassani, M. O.; Germain, A.; Brunel, D.; Commeyras, A., *Tetrahedron Lett.* **1981**, *22*, 65.
7. Taylor, S. L.; Martin, J. C., *J. Org. Chem.* **1987**, *52*, 4147.
8. (a) Forbus, T. R., Jr.; Taylor, S. L.; Martin, J. C., *J. Org. Chem.* **1987**, *52*, 4156. (b) Taylor, S. L.; Forbus, T. R., Jr.; Martin, J. C., *Org. Synth., Coll. Vol.* **1990**, *7*, 506.
9. Gassman, P. G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. P., *J. Am. Chem. Soc.* **1987**, *109*, 2182.
10. (a) Gassman, P. G.; Singleton, D. A., *J. Org. Chem.* **1986**, *51*, 3075. (b) Gorman, D. B.; Gassman, P. G., *J. Org. Chem.* **1995**, *60*, 977.
11. (a) Stang, P. J.; Summerville, R. H., *J. Am. Chem. Soc.* **1969**, *91*, 4600. (b) Summerville, R. H.; Senkler, C. A.; Schleyer, P. v. R.; Dueber, T. E.; Stang, P. J., *J. Am. Chem. Soc.* **1974**, *96*, 1100.
12. García Martínez, A.; Herrera Fernandez Martínez, A.; Alvarez, R.; Silva Losada, M. C.; Molero Vilchez, D.; Subramanian, L. R.; Hanack, M., *Synthesis* **1990**, 881.
13. Olah, G. A.; Wu, A., *J. Org. Chem.* **1991**, *56*, 2531.
14. Narasaka, K.; Kusama, H.; Yamashita, Y.; Sato, H., *Chem. Lett.* **1993**, 489.
15. Okabe, K.; Ohwada, T.; Ohta, T.; Shudo, K., *J. Org. Chem.* **1989**, *54*, 733.
16. Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G., *Synlett* **1990**, 621.
17. Kiso, Y.; Nakamura, S.; Ito, K.; Ukawa, K.; Kitagawa, K.; Akita, T.; Moritoki, H., *J. Chem. Soc., Chem. Commun.* **1979**, 971.
18. Rigo, B.; Cauliez, P.; Fasseur, D.; Couturier, D., *Synth. Commun.* **1988**, *18*, 1247.
19. Launikonis, A.; Sasse, W. H. F.; Willing, I. R., *Aust. J. Chem.* **1993**, *46*, 427.
20. Kawai, M.; Onaka, M.; Izumi, Y., *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1237.
21. Hulin, B.; Koreeda, M., *J. Org. Chem.* **1984**, *49*, 207.
22. Freire, R.; León, E. Z.; Salazar, J. A.; Suárez, E., *J. Chem. Soc., Chem. Commun.* **1989**, 452.
23. Olah, G. A.; Wang, Q.; Sandford, G.; Oxyzoglou, A. B.; Prakash, G. K. S., *Synthesis* **1993**, 1077.
24. Olah, G. A.; Ernst, T. D., *J. Org. Chem.* **1989**, *54*, 1203.
25. Olah, G. A.; Ramaiah, P.; Wang, Q.; Prakash, G. S. K., *J. Org. Chem.* **1993**, *58*, 6900.
26. Olah, G. A.; Ernst, T. D., *J. Org. Chem.* **1989**, *54*, 1204.
27. Childs, R. F.; Shaw, G. S.; Varadarajan, A., *Synthesis* **1982**, 198.
28. Marsmann, H. C.; Horn, H. G., *Z. Naturforsch., Tell B* **1972**, *27*, 1448.
29. Demuth, M.; Mikhail, G., *Synthesis* **1982**, 827.
30. Uhlig, W., *J. Organomet. Chem.* **1993**, *452*, 29.
31. Barluenga, J.; González, J. M.; García-Martín, M. A.; Campos, P. J.; Asensio, G., *J. Org. Chem.* **1993**, *58*, 2058.
32. Bullock, R. M.; Rappoli, B. J., *J. Chem. Soc., Chem. Commun.* **1989**, 1447.
33. Olah, G. A.; Wu, A.-H., *Synthesis* **1991**, 407.
34. Olah, G. A.; Wang, Q.; Orlinkov, A.; Ramaiah, P., *J. Org. Chem.* **1993**, *58*, 5017.
35. Stevens, M. F. G.; Chui, W. K.; Castro, M. A., *J. Heterocycl. Chem.* **1993**, *30*, 849.
36. Brown, L.; Koreeda, M., *J. Org. Chem.* **1984**, *49*, 3875.
37. Takeuchi, K.; Ohga, Y.; Munakata, M.; Kitagawa, T.; Kinoshita, T., *Tetrahedron Lett.* **1992**, *33*, 3335.
38. Booth, B. L.; El-Fekky, T. A., *J. Chem. Soc., Perkin Trans. 1* **1979**, 2441.
39. Effenberger, F.; Klenk, H.; Reiter, P. L., *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 775.
40. Auzanneau, F.-I.; Bundle, D. R., *Can. J. Chem.* **1993**, *71*, 534.
41. Marson, C. M.; Fallah, A., *Tetrahedron Lett.* **1994**, *35*, 293.
42. Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K., *J. Am. Chem. Soc.* **1994**, *116*, 2312.
43. Pearson, W. H.; Fang, W.; Kamp, J. W., *J. Org. Chem.* **1994**, *59*, 2682.
44. Olah, G. A., *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 767.
45. Olah, G. A.; Klumpp, D. A., *Acc. Chem. Res.* **2004**, *37*, 211.
46. Suzuki, T.; Ohwada, T.; Shudo, K., *J. Am. Chem. Soc.* **1997**, *119*, 6774.
47. Prakash, G. K. S.; Yan, P.; Török, B.; Olah, G. A., *Catal. Lett.* **2003**, *87*, 109; *89*, 159.
48. Rendy, R.; Zhang, Y.; McElrea, A.; Gomez, A.; Klumpp, D. A., *J. Org. Chem.* **2004**, *69*, 2340.
49. Klumpp, D. A.; Garza, M.; Lau, S.; Shick, B.; Kantardjieff, K., *J. Org. Chem.* **1999**, *64*, 7635.

50. Hwang, J. P.; Prakash, G. K. S.; Olah, G. A., *Tetrahedron* **2000**, *56*, 7199.
51. Ohwada, T.; Suzuki, T.; Shudo, K., *J. Am. Chem. Soc.* **1998**, *120*, 4629.
52. Klumpp, D. A.; Garza, M.; Jones, A.; Mendoza, S., *J. Org. Chem.* **1999**, *64*, 6702.
53. Klumpp, D. A.; Garza, M.; Sanchez, G. V., Jr.; Lau, S.; de Leon, S., *J. Org. Chem.* **2000**, *65*, 8997.
54. Klumpp, D. A.; Aguirre, S. L.; Sanchez, G. V., Jr.; de Leon, S., *J. Org. Lett.* **2001**, *3*, 2781.
55. Klumpp, D. A.; Sanchez, G. V., Jr.; Aguirre, S. L.; Zhang, Y.; de Leon, S., *J. Org. Chem.* **2002**, *67*, 5028.
56. Zhang, Y.; McElrea, A.; Sanchez, G. V., Jr.; Do, D.; Gomez, A.; Aguirre, S. L.; Rendy, R.; Klumpp, D. A., *J. Org. Chem.* **2003**, *68*, 5119.
57. Klumpp, D. A.; Rendy, R.; Zhang, Y.; Gomez, A.; McElrea, A., *Org. Lett.* **2004**, *6*, 1789.
58. Anderson, K. W.; Tepe, J. J., *Tetrahedron* **2002**, *58*, 8475.
59. Koltunov, K. Y.; Walspurger, S.; Sommer, J., *Eur. J. Org. Chem.* **2004**, *19*, 4039.
60. Klumpp, D. A.; Rendy, R.; McElrea, A., *Tetrahedron Lett.* **2004**, *45*, 7959.
61. Klumpp, D. A.; Rendy, R.; Zhang, Y.; McElrea, A.; Gomez, A.; Dang, H., *J. Org. Chem.* **2004**, *69*, 8108.
62. Klumpp, D. A.; Kindelin, P. J.; Li, A., *Tetrahedron Lett.* **2005**, *46*, 2931.
63. Zhang, Y.; Briski, J.; Zhang, Y.; Rendy, R.; Klumpp, D. A., *Org. Lett.* **2005**, *7*, 2505.
64. Prakash, G. K. S.; Yan, P.; Török, B.; Olah, G. A., *Synlett* **2003**, 527.
65. Shamma, T.; Buchholz, H.; Prakash, G. K. S.; Olah, G. A., *Isr. J. Chem.* **1999**, *39*, 207.
66. Olah, G. A.; Marinez, E. R.; Prakash, G. K. S., *Synlett* **1999**, 1397.
67. Repichet, S.; Le Roux, C.; Dubac, J., *Tetrahedron Lett.* **1999**, *40*, 9233.
68. Peyronneau, M.; Boisdon, M-T.; Roques, N.; Mazieres, S.; Le Roux, C., *Eur. J. Org. Chem.* **2004**, *22*, 4636.
69. Corey, E. J.; Shibata, T.; Lee, T. W., *J. Am. Chem. Soc.* **2002**, *124*, 3808.
70. Aggarwal, V. K.; Vennall, G. P.; Davey, P. N.; Newman, C., *Tetrahedron Lett.* **1997**, *38*, 2569.
71. Villemin, D.; Bar, N.; Hammadi, M., *Tetrahedron Lett.* **1997**, *38*, 4777.
72. Nakajima, T.; Segi, M.; Mituoka, T.; Fukute, Y.; Honda, M.; Naitou, K., *Tetrahedron Lett.* **1995**, *36*, 1667.
73. Kitamura, T.; Nagata, K.; Taniguchi, H., *Tetrahedron Lett.* **1995**, *36*, 1081.
74. Kitamura, T.; Inoue, D.; Wakimoto, I.; Nakamura, T.; Katsuno, R.; Fujiwara, Y., *Tetrahedron* **2004**, *60*, 8855.
75. Olah, G. A.; Batamack, P.; Deffieux, D.; Torok, B.; Wang, Q.; Molnar, A.; Prakash, G. K. S., *Appl. Catalysis A: General* **1996**, *146*, 107.
76. Nikolopoulos, A. A.; Kogelbauer, A.; Goodwin, J. G., Jr.; Marcelin, G., *J. Catalysis* **1996**, *158*, 76.
77. de Angelis, A.; Flego, C.; Ingallina, P.; Montanari, L.; Clerici, M. G.; Carati, C.; Perego, C., *Catalysis Today* **2001**, *65*, 363.
78. Marziano, N. C.; Ronchin, L.; Tortato, C.; Zingales, A.; Sheikh-Osman, A. A., *J. Molecular Catalysis A: Chemical* **2001** *, 174*, 265.
79. Chidambaram, M.; Curulla-Ferre, D.; Singh, A. P.; Anderson, B. G., *J. Catalysis* **2003**, *220*, 442.
80. Landge, S. M.; Chidambaram, M.; Singh, A. P., *J. Molecular Catalysis A: Chemical* **2004**, *213*, 257.
81. Xu, B.-Q.; Sood, D. S.; Gelbaum, L. T.; White, M. G., *J. Catalysis* **1999**, *186*, 345.
82. Xu, B.-Q.; Sood, D. S.; Iretskii, A. V.; White, M. G., *J. Catalysis* **1999**, *187*, 358.
83. Sood, D. S.; Sherman, S. C.; Iretskii, A. V.; Kenvin, J. C.; Schiraldi, D. A.; White, M. G., *J. Catalysis* **2001**, *199*, 149.
84. Al-kinany, M. C.; Jibril, B. Y.; Al-Khowaiter, S. H.; Al-Dosari, M. A.; Al-Megren, H. A.; Al-Zahrani, S. M.; Al-Humaizi, K., *Chem. Eng. & Proc.* **2005**, *44*, 841.
85. Laali, K. K.; Sarca, V. D.; Okazaki, T.; Brock, A.; Der, P., *Org. & Biomol. Chem.* **2005**, *3*, 1034.
86. Huang, J.-W.; Shi, M., *Synlett* **2004**, 2343.
87. Coulombel, L.; Dunach, E., *Green Chem.* **2004**, *6*, 499.
88. Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T., *Org. Lett.* **2002**, *4*, 2389.
89. Ishimaru, K.; Kojima, T., *Tetrahedron Lett.* **2003**, *44*, 5441.
90. Colquhoun, H. M.; Lewis, D. F.; Williams, D. J., *Org. Lett.* **2001**, *3*, 2337.
91. Arisawa, M.; Yamaguchi, M., *Org. Lett.* **2001**, *3*, 763.
92. Dumeunier, R.; Marko, I. E., *Tetrahedron Lett.* **2004**, *45*, 825.
93. Mahoney, J. M.; Smith, C. R.; Johnston, J. N., *J. Am. Chem. Soc.* **2005**, *127*, 1354.

Trifluoromethanesulfonic Anhydride



[358-23-6] $C_2F_6O_5S_2$ (MW 282.16)
InChI = 1/C2F6O5S2/c3-1(4,5)14(9,10)13-15(11,12)2(6,7)8
InChIKey = WJKHJLXJJJATHN-UHFFFAOYAC

(preparation of triflates;[1] mild dehydrating reagent; promoter for coupling reactions in carbohydrates[2])

Alternate Name: triflic anhydride.
Physical Data: bp 81–83 °C/745 mmHg; *d* 1.677 g cm^{-3}; n_D^{20} 1.3210.
Solubility: soluble in dichloromethane; insoluble in hydrocarbons.
Form Supplied in: colorless liquid in ampules. Once opened it should be immediately used.
Analysis of Reagent Purity: IR, NMR.
Preparative Methods: by distillation of trifluoromethanesulfonic acid with an excess of phosphorus (V) oxide.[1]
Purity: by redistillation with a small amount of P_2O_5. It is advisable to freshly distill the reagent from a small quantity of P_2O_5 before use.
Handling, Storage, and Precaution: the pure reagent is a colorless liquid that does not fume in air and is stable for a long period. It is not soluble in water and hydrolyzes only very slowly to triflic acid over several days at room temperature. Preferably stored under N_2 in a stoppered flask. Dangerously exothermic reactions have been reported when attempting to triflate hindered alcohols.[67]

Original Commentary

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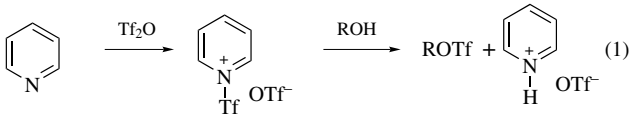
Reaction with Alcohols and Phenols. The reaction of alcohols and phenols with triflic anhydride (Tf_2O) at ~0 °C in the presence of a base (usually pyridine) in an inert solvent (usually dichloromethane) for 2–24 h affords the corresponding reactive trifluoromethanesulfonate esters (triflates).[1] When triflic

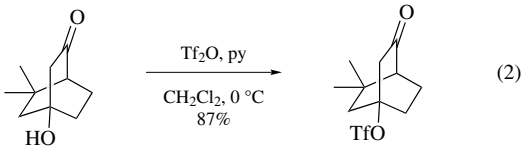
anhydride and pyridine are combined, the pyridinium salt forms immediately and normally precipitates out from the reaction mixture. Nevertheless, the salt is an effective esterifying agent, reacting with the added alcohol to give triflates in high yields (eq 1).[3]



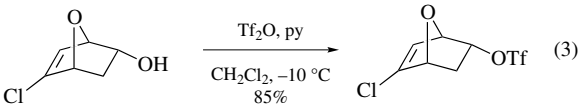
(1)

R = alkyl, aryl

Pyridine can become involved in nucleophilic substitution when very reactive triflates are being synthesized.[2,3] One approach to minimize this disadvantage is to replace it with sterically hindered bases, such as 2,6-di-*t*-butyl-4-methylpyridine,[3,4] 2,4,6-trisubstituted pyrimidines,[5] or nonnucleophilic aliphatic amines (usually *N,N*-diisobutyl-2,4-dimethyl-3-pentylamine). No salt formation appears to take place under these conditions. The triflic anhydride seems to be the direct triflating agent and the base only neutralizes the triflic acid formed. Numerous alkyl triflates have been prepared in the literature[1b] by the above method. Some recent examples of triflates prepared from alcohols are illustrated in eqs 2 and 3.[6,7] As an exception, 2,6-dinitrobenzyl alcohol does not react with Tf_2O although similar sulfonyl esters could be prepared.[8]

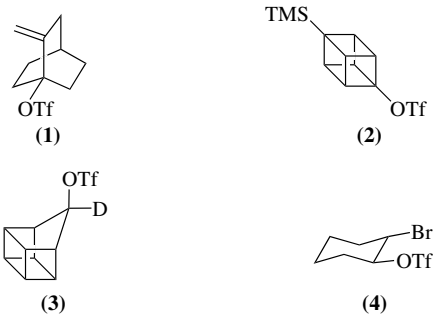


(2)



(3)

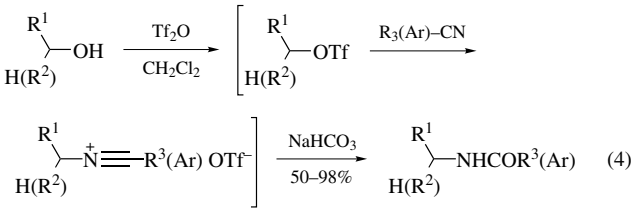
Alkyl triflates have come to be recognized as useful intermediates for the functionalization of organic substrates by nucleophilic substitution, e.g. in carbohydrate chemistry.[9] Triflate is the best leaving group known[1b] next to the nonaflate and hence a large number of triflates, obtained in good yields by reaction of the corresponding alcohols (or alkoxides) with Tf_2O, have been used to generate unstable or destabilized carbocations under solvolytic conditions.[1b] Some new typical examples are shown in (**1**)–(**4**).[10–13]



(**1**) (**2**) (**3**) (**4**)

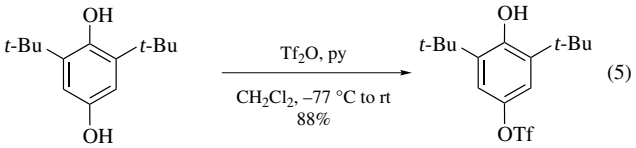
Alkyl triflates are known to be powerful reagents for the alkylation of aromatic compounds.[1b,14] However, the reaction of alkyl triflates with heterocycles affords *N*-alkylation products.[15]

In an improved modification of the Ritter reaction, primary and secondary alcohols react with Tf_2O in CH_2Cl_2 in the presence of a 2:1 excess of nitriles to give the corresponding amides in good yields (eq 4).[16]

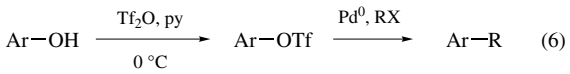


(4)

Aryl triflates are prepared from phenols at 0 °C using pyridine as solvent.[1b] Sometimes it is useful to conduct the reaction in CH_2Cl_2 at −77 °C, as in the preparation of 3,5-di-*t*-butyl-4-hydroxyphenyl triflate (eq 5).[17] Aryl triflates are synthetically transformed into several products of interest and applications in organic chemistry, by cross-coupling reactions with organometallics (eqs 5 and 6).[18]

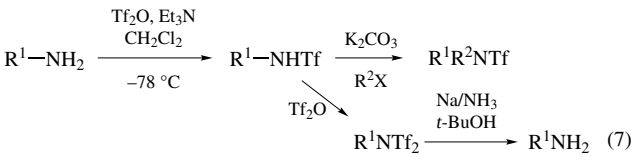


(5)



(6)

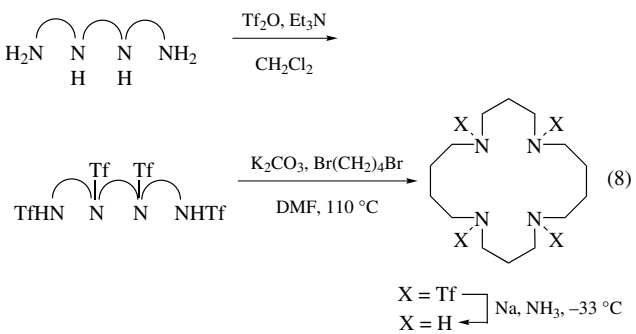
Reaction of Tf_2O with Amines. The reaction of 1 equiv of Tf_2O in CH_2Cl_2 and Et_3N with amines (or their salts) affords trifluoromethanesulfonamides (triflamides) in good yields.[19,20] If 2 equiv of Tf_2O are used, triflimides are formed. The triflamides are soluble in alkali and readily alkylated to triflimides (eq 7).[19,20]



(7)

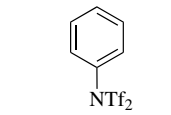
$R^1 = R^2$ = alkyl

Triflamides can be deprotected reductively (sodium–ammonia) to yield the corresponding amines.[21] This protocol has been employed in the facile two-step synthesis of aza macrocycles starting from trifluoromethanesulfonyl derivatives of linear tetramines (eq 8).[22]

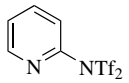


(8)

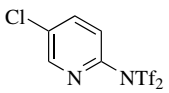
Several triflamides (**5**–**8**)[23] and *O*-triflylammonium salts[24] have been used for the formation of vinyl triflates from regiospecifically generated metalloenolates or for preparing triflates from alcohols.



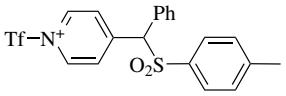
(5)



(6)

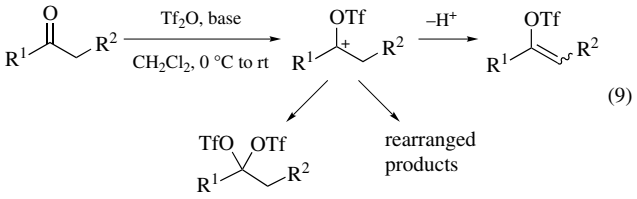


(7)



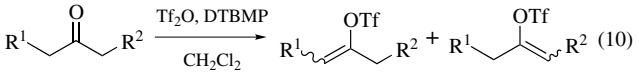
(8)

Reaction of Tf_2O with Carbonyl Compounds. The reaction of Tf_2O with carbonyl compounds consists of the electrophilic attack of the anhydride on the carboxylic oxygen, resulting in the formation of triflyloxycarbenium ions as intermediates (eq 9). According to the nature of the carbonyl compound, the triflyloxycarbenium cations can eliminate a proton giving a vinyl triflate, undergo a rearrangement, or be trapped by the gegenion yielding *gem*-bistriflates (eq 9).



(9)

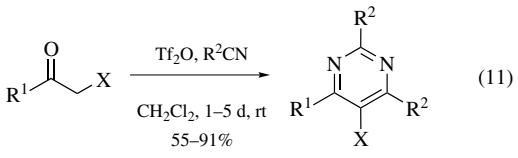
In the case of acyclic and monocyclic ketones, the reaction with Tf_2O affords vinyl triflates in good yields. Several methods exist to realize this reaction.[1b,25] For example, the reaction is carried out at room temperature in CH_2Cl_2 (or pentane) in the presence of 2,4-di-*t*-butyl-4-methylpyridine (DTBMP) (eq 10).[4]



(10)

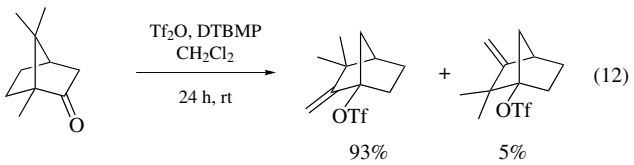
Other bases such as pyridine,[1b] lutidine,[1b] Et_3N,[1b] polymer-bound 2,6-di-*t*-butyl-4-methylpyridine,[26] and 2,4,6-trialkyl-substituted pyrimidines[27] were also used. The commercially available *N*,*N*-diisobutyl-2,4-dimethyl-3-pentylamine is a very convenient base to prepare the vinyl triflates.[28] In the case of nonfunctionalized ketones, anhydrous Na_2CO_3 has been proved to be very successful.[1b,25]

The reaction of ketones with Tf_2O is governed by Markovnikov's rule and results in the formation of the more substituted triflate as the major product. When the reaction of ketones[27] and α-halo ketones[29] with Tf_2O is carried out in the presence of a nitrile, the intermediate trifloxy cation (eq 9) can be trapped, forming pyrimidines in good yields (eq 11).



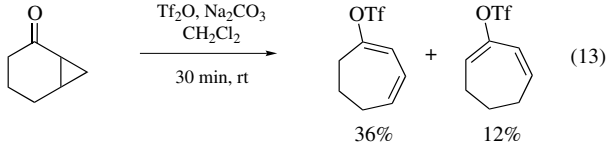
(11)

The reaction of Tf_2O with strained bicyclic ketones such as 2-norbornanone and nopinone takes place with Wagner–Meerwein rearrangement of the corresponding triflyloxy cations, forming bridgehead triflates in good yields (eq 12).[30] These triflates are key compounds in the preparation of other bridgehead derivatives by substitution[31] and of substituted cyclopentanes by fragmentation.[32]

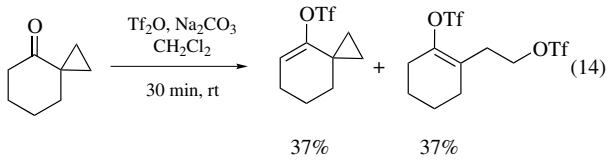


(12)

In the reaction of Tf_2O with norcaranones and spiro[2.5]octan-4-one, the cyclopropane ring undergoes fragmentation to give vinyl triflates (eqs 13 and 14). [33]

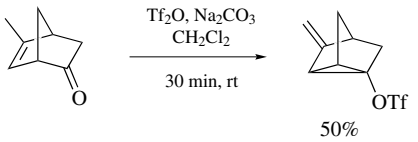


(13)



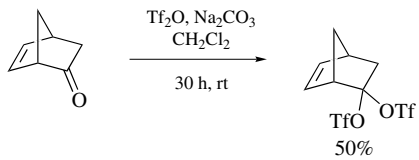
(14)

However, a cyclopropane ring is formed in the reaction of 5-methylnorborn-5-en-2-one with Tf_2O under the same conditions (eq 15).[34]

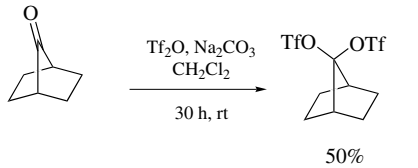


(15)

When the ketone can accomplish neither the stereoelectronic conditions for the elimination of TfOH nor for a rearrangement, the reaction of ketones with Tf_2O results in the formation of a *gem*-bistriflate (eqs 16 and 17).[35]

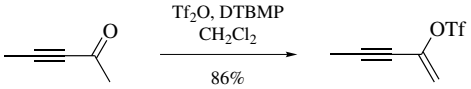


(16)



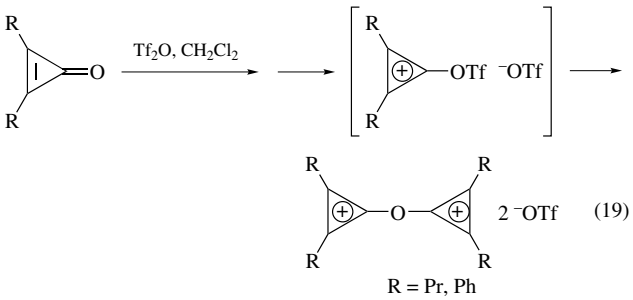
(17)

Sensitive ketones such as 3-pentyn-2-one also afford the corresponding vinyl triflate on treatment with Tf_2O in the presence of a base (eq 18).[36]



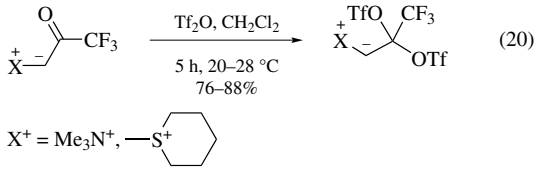
(18)

Substituted cyclopropenones and tropones react with Tf_2O with the formation of the corresponding dication ether salts (eq 19).[37]



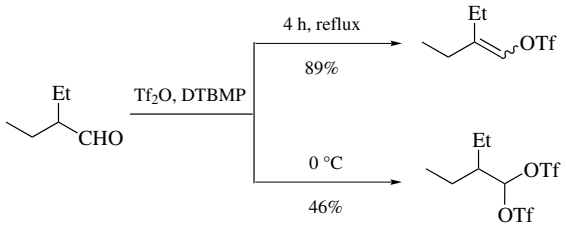
(19)

Treatment of trifluoroacetyl ylides with Tf_2O results in the formation of *gem*-bistriflates (eq 20).[38]



(20)

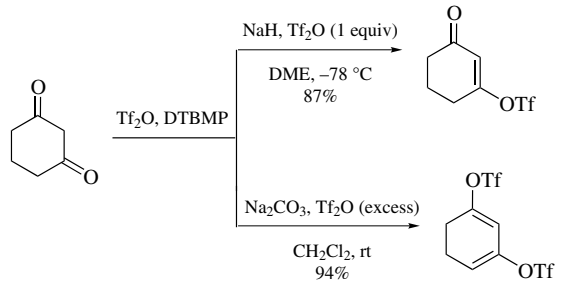
Reaction of Tf_2O with Aldehydes. The reaction of aliphatic aldehydes with Tf_2O in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) in refluxing CH_2Cl_2 or $ClCH_2CH_2Cl$ for 2 h affords the corresponding vinyl triflates as a mixture of (*Z*)- and (*E*)-isomers.[4,39] When the reaction is carried out at 0 °C, *gem*-bistriflates are formed as products (eq 21).[40] The *gem*-bistriflates result due to the trapping of the intermediate triflyloxycarbenium ion by the triflate anion. Primary vinyl triflates have been used extensively in the generation of alkylidene carbenes,[41] and *gem*-bistriflates are interesting precursors for *gem*-dihaloalkanes[42,43] and (*E*)-iodoalkenes.[44]



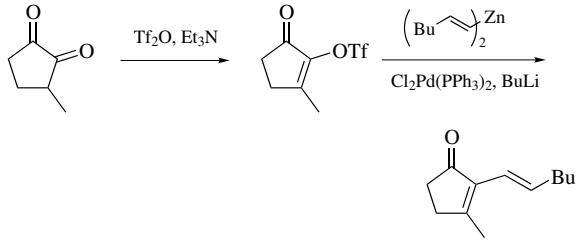
(21)

Reaction with Dicarbonyl Compounds. 1,3-Diketones can be reacted with an equimolar amount of Tf_2O or in excess to furnish the corresponding vinyl triflates or dienyl triflates (eq 22).[45] These triflates are transferred into monoketones, monoalcohols, alkanes, and unsaturated ketones by means of various reducing reagents.[45]

The reaction of 3-methylcyclopentane-1,2-dione with Tf_2O/Et_3N affords the vinyl triflate in 53% yield (eq 23).[46] The reaction takes place probably through the enol form. The product was coupled with alkenylzinc compounds in the presence of a palladium catalyst.[46]

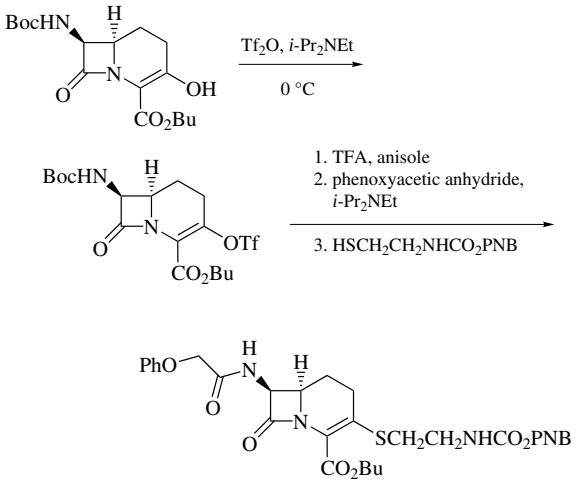


(22)



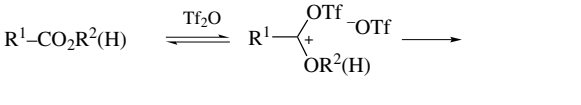
(23)

The reaction of β-keto esters[47] with Tf_2O in the presence of a base results in the formation of 2-carboxyvinyl triflates (eq 24). These substrates undergo nucleophilic substitution of the TfO-group (eq 24)[47] and also coupling reactions.[48]



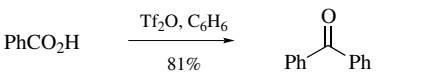
(24)

Reaction with Carboxylic Acids and Esters. The reaction of carboxylic acids and esters with Tf_2O takes place according to the scheme shown in (eq 25).[49]



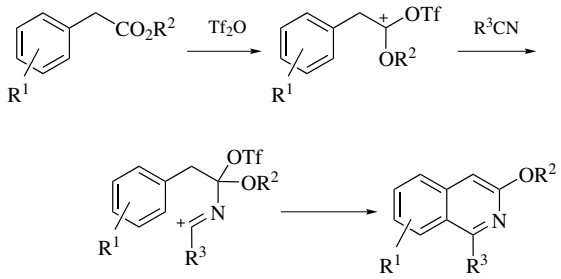
(25)

The trifluoromethanesulfonic carboxylic anhydrides are highly effective acylation agents, which react without catalysts even with deactivated aromatics to yield aryl ketones (eq 26).[50]



(26)

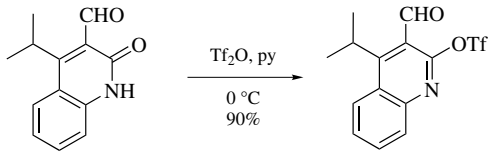
Alkyl arylacetates react with Tf_2O to give a cation which in the presence of a nitrile affords isoquinoline derivatives via cyclization of the intermediate nitrilium cation (eq 27).[50]



(27)

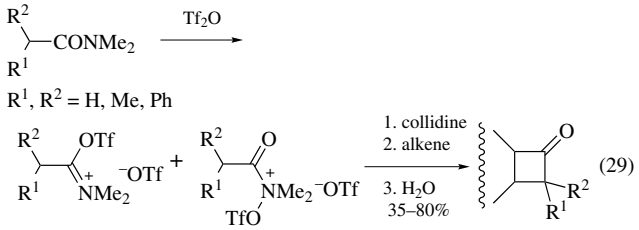
R^1 = H, 6-Me, 7–Cl, 5–NO_2, 6,7-$(OMe)_2$; R^2 = Et, Me

Reaction of Tf_2O with Amides. The reaction of a 2-oxo-1,2-dihydroquinoline with Tf_2O in the presence of pyridine affords the corresponding 2-quinoline triflate (eq 28).[51]



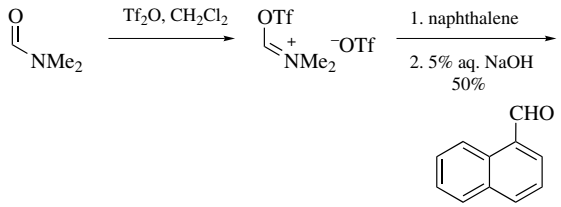
(28)

The reaction of tertiary amides with Tf_2O gives a mixture of *O*-sulfonylated (major) and *N*-sulfonylated (minor) products. In the presence of collidine and an alkene, [2 + 2] cycloadducts are formed which hydrolyze to give cyclobutanones (eq 29).[52]



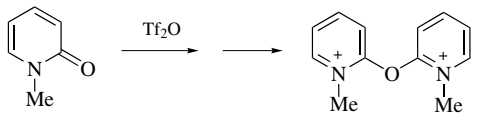
(29)

Treatment of DMF with Tf_2O results in the formation of an imminium triflate, which formylates less active aromatics. It is a convenient variation of the Vilsmeier–Haack reaction (eq 30).[53]

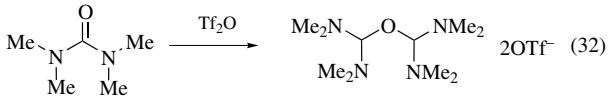


(30)

The reaction of *N*-methylpyridone and substituted urea systems with Tf_2O gives heteroatom-stabilized dicarbonium salts (eqs 31 and 32).[37,54]

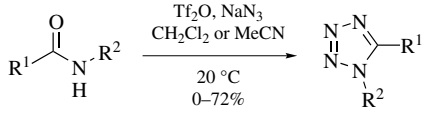


(31)



(32)

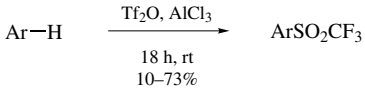
Secondary amides can be converted to tetrazoles with Tf_2O in the presence of sodium azide (eq 33).[55]



(33)

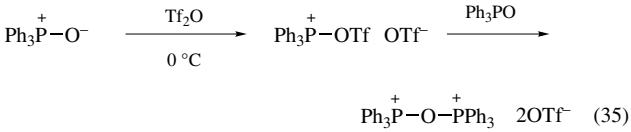
R^1 = alkyl, Ph; R^2 = alkyl, $(CH_2)_2OAc$, $(CH_2)_2OTBDMS$

Other Applications. Activated arenes can be converted to aryl triflones by Friedel–Crafts reaction with Tf_2O using aluminum chloride as catalyst (eq 34).[56]



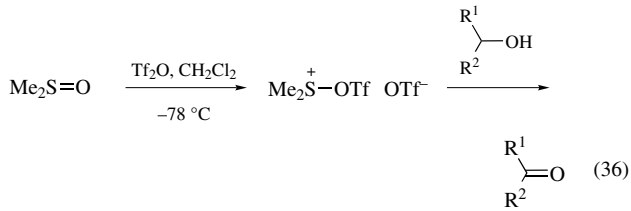
(34)

The reaction of Tf_2O with Ph_3PO in CH_2Cl_2 at 0 °C affords triphenylphosphine ditriflate, which can be used as an oxygen activator, and then to a diphosphonium salt (eq 35).[57]



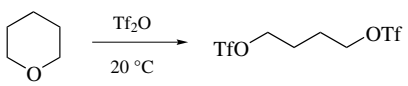
(35)

The less stable dimethyl sulfide ditriflate, obtained from Tf_2O and DMSO, has been used to oxidize alcohols (eq 36).[58]



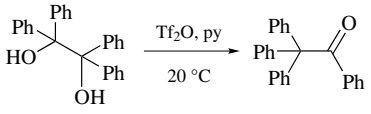
(36)

Tetrahydropyran is not a suitable solvent in reactions involving Tf_2O because it is cleaved, affording 1,5-bistrifloxypentane (eq 37).[59]



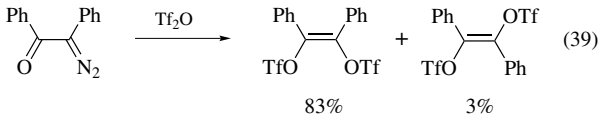
(37)

Diols react with Tf_2O to yield the corresponding ditriflates; however, the reaction of 1,1,2,2-tetraphenyl-1,2-ethanediol with Tf_2O takes place with rearrangement (eq 38).[59]



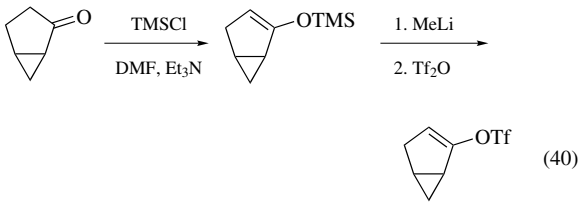
(38)

Vinylene 1,2-bistriflates are formed by the reaction of azobenzils with Tf_2O (eq 39).[60]



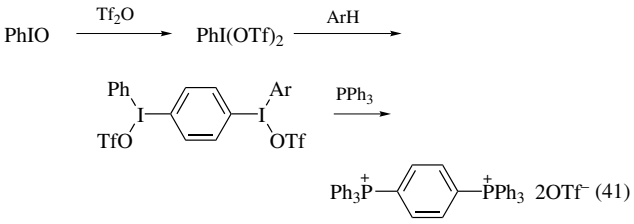
(39)

The reaction of enolates, prepared from silyl enol ethers and methyllithium, with Tf_2O affords vinyl triflates (eq 40).[61]



(40)

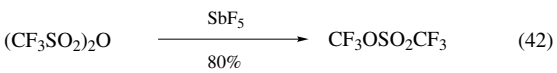
The combination of equimolecular quantities of iodosylbenzene and Tf_2O generates $PhI(OTf)_2$, a compound also formed by treatment of Zefiro's reagent with Tf_2O. As shown in eq 41, this compound can be used to prepare *para*-disubstituted benzene derivatives in good yields.[62]



(41)

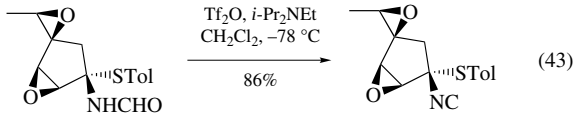
Tf_2O is a suitable promoter for the stereoselective glucosidation of glycosyl acceptors using sulfoxides as donors.[63]

The reaction of Tf_2O with a catalytic amount of antimony(V) fluoride at 25 °C produces trifluoromethyl triflate in 94% yield (eq 42).[64]



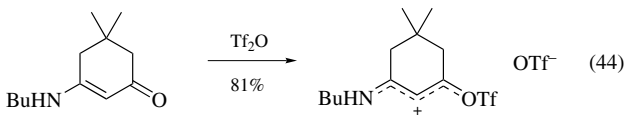
(42)

Useful application of Tf_2O as dehydrating reagent is accounted by the synthesis of isocyanides from formamides and vinylformamides (eq 43).[65]



(43)

Reaction of enaminones with Tf_2O in a 1:1 molar ratio affords 3-trifloxypropeniminium triflates by *O*-sulfonylation. From a cyclic enaminone, by using a 2:1 molar ratio, the corresponding bis(3-amino-2-propenylio) bistriflate is obtained (eq 44).[66]



(44)

First Update

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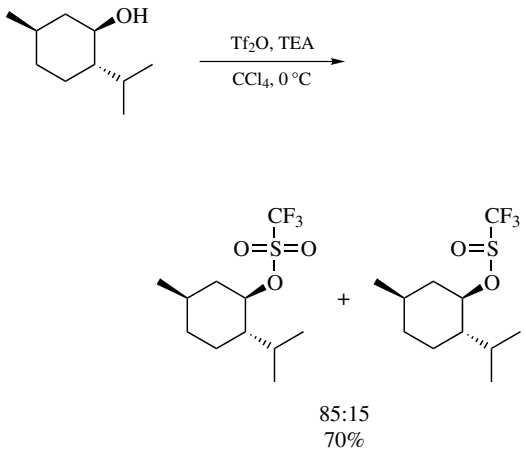
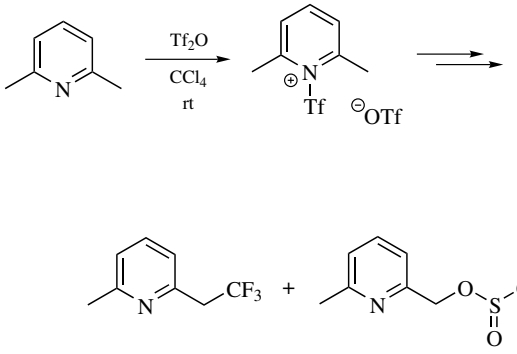
Reactions with Alcohols, Phenols, and Thiols. Chemical transformations effected by triflic anhydride have been comprehensively reviewed.[68] Formation of alkyl triflates from alcohols is typically performed using triflic anhydride (Tf_2O) and pyridine or hindered pyridines such as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) according to the methods already outlined. Purification of the resultant triflate from the excess base can sometimes prove problematic, and polymeric pyridine equivalents such as poly(4-vinylpyridine) or poly(2,6-di-*tert*-butylpyridine) have been successfully used allowing the removal of excess base and its triflate salt by simple filtration.[69] Alternatively, phenolic triflates can be prepared from Tf_2O under Schotten–Baumann conditions using toluene and 30% aqueous K_3PO_3.[70] Work-up is effected by simple separation of the organic phase and evaporation of the solvent. When attempting to triflate alcohols of low reactivity with Tf_2O, alternative redox processes can occur resulting in the formation of sulfinates as the major products. Such undesired redox processes are favored at higher temperatures and particularly when using triethylamine as base (eq 45).[67]



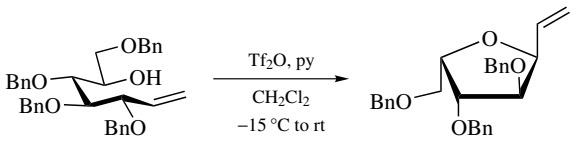
(45)

Methyl substituted pyridines such as 2,6-lutidine and 2,4,6-collidine can also afford undesirable by-products. These pyridines can react with Tf_2O to generate sulfinate- and trifluoromethyl-substituted derivatives (eq 46).[71] In such cases, the use of 2,6-di-*tert*-butyl-substituted pyridines is recommended.



(46)

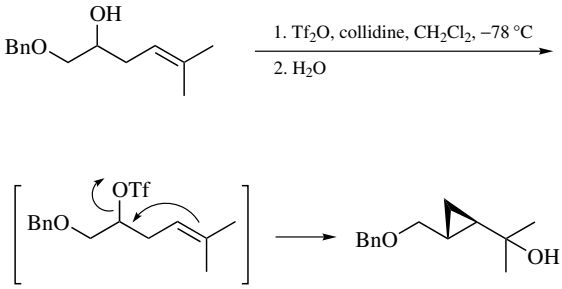
Triflates formed from hept-1-enitols spontaneously cyclize with debenzylation to afford vinyl C-glycosides (eq 47).[72,73]



(47)

90%

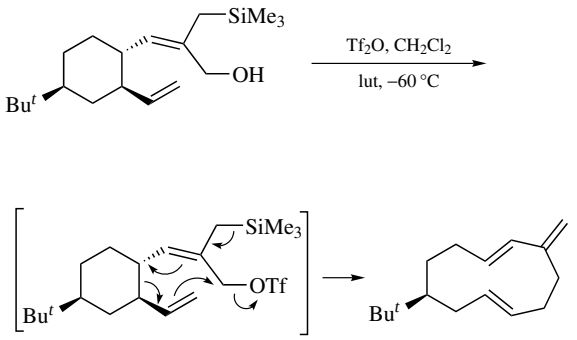
Dimethyl substituted homoallylic alcohols undergo smooth cyclization to *trans*-cyclopropanes upon treatment with Tf_2O and a base (eq 48).[74,75] Various functionalities can be introduced adjacent to the newly formed cyclopropane ring by altering the quenching conditions.[74]



(48)

87%

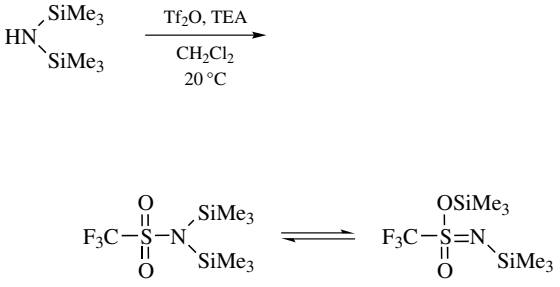
Eleven-membered carbocycles are formed by way of a five-carbon ring expansion in a homo-Cope rearrangement upon treatment of β-(hydroxymethyl)allylsilanes with Tf_2O (eq 49).[76]



(49)

75%

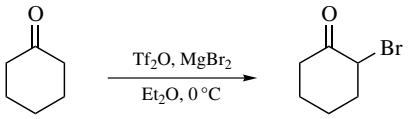
Reaction with Amines. Reaction of Tf_2O with hexamethyldisilazane affords the reactive silylating reagent *N*,*N*-bis(trimethylsilyl)trifluoromethylsulfonamide.[77,78] This compound exists in two tautomeric forms in solution, related by trimethylsilyl shifts between oxygen and nitrogen (eq 50).[77]



(50)

85%

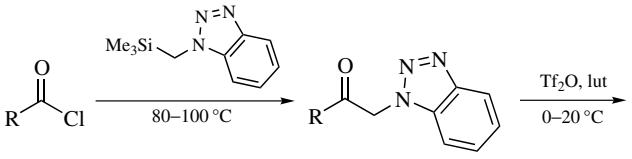
Reaction with Carbonyl and Thiocarbonyl Compounds. Treatment of ketones having α-protons with Tf_2O and magnesium bromide or Grignard reagents results in α-bromination (eq 51).[79]

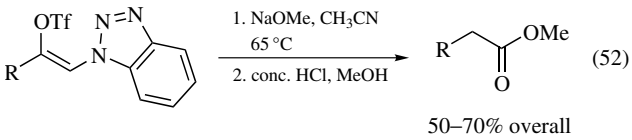


(51)

89%

An alternative to the Arndt–Eistert reaction for the homologation of carboxylic acids uses *N*-(acylmethyl)benzotriazoles prepared from acyl chlorides and *N*-(trimethylsilyl)methylbenzotriazole. Upon treatment with Tf_2O these compounds are converted to the corresponding vinyl triflate, and then to the homologous ester by sequential treatment with sodium methoxide in acetonitrile and then HCl in methanol (eq 52).[80]

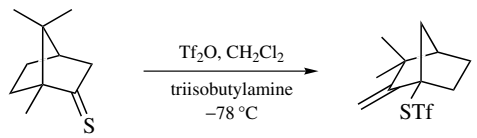




(52)

50–70% overall

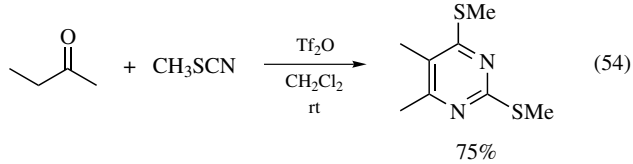
Tf_2O reacts with thioketones to generate triflylthiocarbenium ions that undergo Wagner–Meerwein rearrangement to bridgehead thiotriflates (eq 53).[81]



(53)

79%

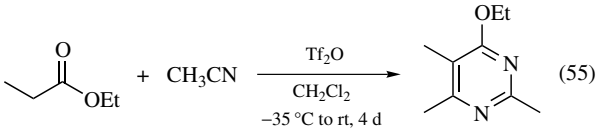
Ketones react with methylthiocyanate in the presence of Tf_2O to afford 2,4-bis(methylthio)pyrimidines (eq 54).[82] Methylthio substituted pyrimidines are useful synthetic intermediates as the methylthio groups can be substituted by other functionalities such as alkoxy and amino groups. Substitution occurs faster at the 4-position, allowing the selective introduction of two different nucleophiles.[68,82]



(54)

75%

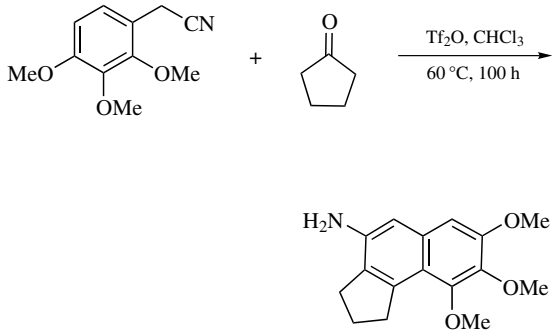
When the reaction is carried out with an ester and a nitrile, good yields of 4-alkoxypyrimidines are obtained (eq 55).[83]



(55)

75%

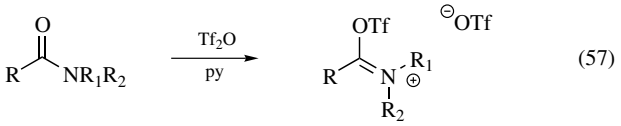
Ketones and nitriles when treated with Tf_2O react to give pyrimidines as outlined earlier (eq 11). In the case of benzyl nitriles bearing electron-donating substitutents, naphthalene derivatives are obtained instead (eq 56).[84]



(56)

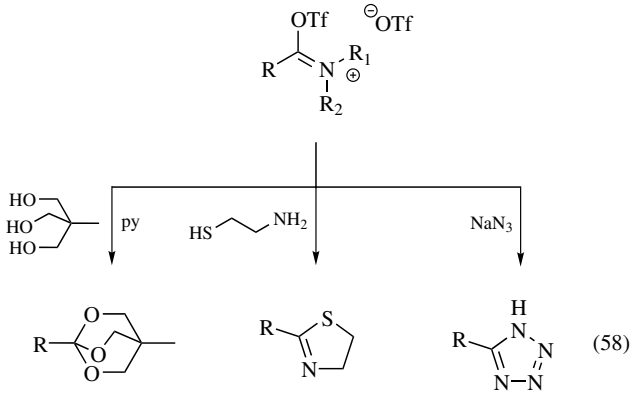
23%

Reaction with Amides. It is well known that treatment of secondary or tertiary amides with Tf_2O affords imino and iminium triflates, respectively (eq 57).



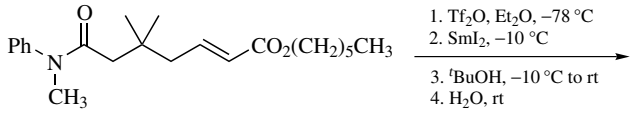
(57)

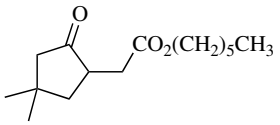
These salts can react with a variety of nucleophiles including amines (to afford amidines),[85–87] alcohols (to afford esters),[85,88] hydrogen sulfide (to afford thioamides),[89] and isotopically labeled water (to afford ^{18}O-labeled amides).[89] Iminium triflates are also excellent intermediates for the preparation of assorted heterocycles. Iminium triflates react with azides (to afford tetrazoles),[55] β-mercaptoamines (to afford thiazolines),[90] and triols (to afford orthoesters) (eq 58).[91] The reaction of lactams with Tf_2O and sodium azide affords tetrazolo-fused bicyclics.[92]



(58)

Treatment of unsaturated amides with Tf_2O generates intermediate iminium triflates that cyclize under radical conditions (eq 59).[93]

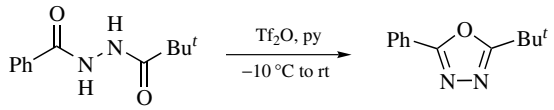




(59)

68%

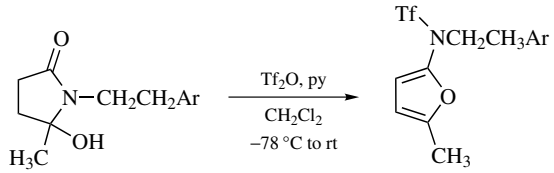
Treatment of bis-hydrazides with Tf_2O and pyridine provides a mild method for the formation of 1,3,4-oxadiazoles (eq 60).[94]



(60)

71%

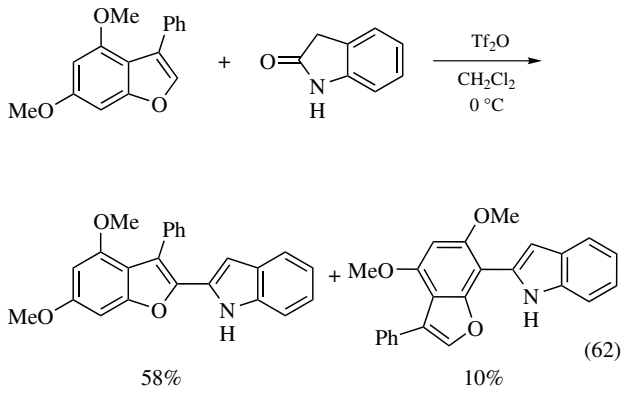
Carbinolamides (derived from keto amides) afford 2-sulfonamido-substituted furans when treated with Tf_2O and pyridine (eq 61).[95]



(61)

90%

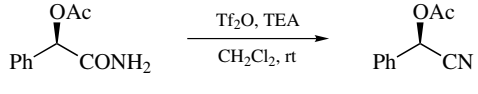
Indolin-2-ones can participate in Vilsmeier reactions with reactive aromatics under the agency of Tf_2O. In the reaction with indoles and benzofurans, Tf_2O was found to be the reagent of choice; no reaction took place when phosphorous oxychloride was used (eq 62).[96]



(62)

58% 10%

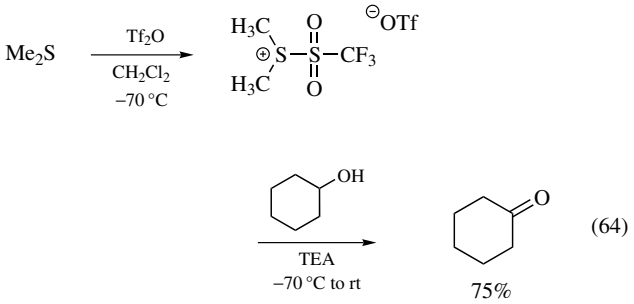
Tf_2O and a base can effect dehydration of primary amides to nitriles.[97] This procedure is particularly mild, with no epimerization observed at the stereogenic α-carbon of several substrates (eq 63).[97]



(63)

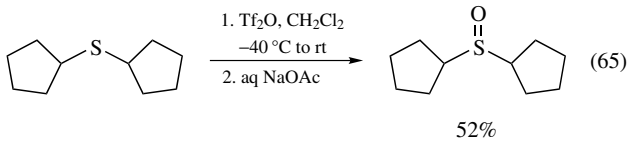
85%

Oxidations. Tf_2O reacts with sulfides affording a trifluoromethylsulfonylsulfonium triflate, which can be used to oxidize alcohols (eq 64).[98]



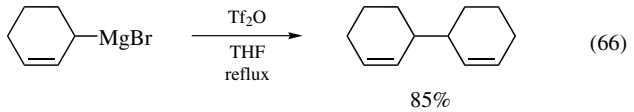
(64)

Alternatively, the intermediate sulfonium salts prepared in the same manner can be treated with aqueous sodium acetate to afford the sulfoxide; none of the corresponding sulfones were observed (eq 65).[98]



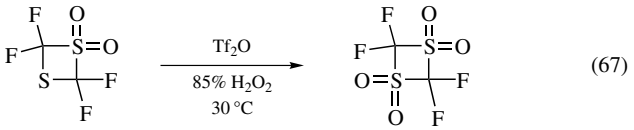
(65)

Tf_2O reacts with Grignard reagents to afford the self-coupled alkanes (eq 66).[99]



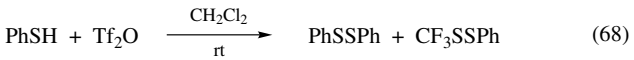
(66)

Addition of Tf_2O to 85% hydrogen peroxide affords the powerful oxidant trifluoromethanepersulfonic acid. This oxidant will convert unreactive thioethers to the corresponding sulfones (eq 67).[100]



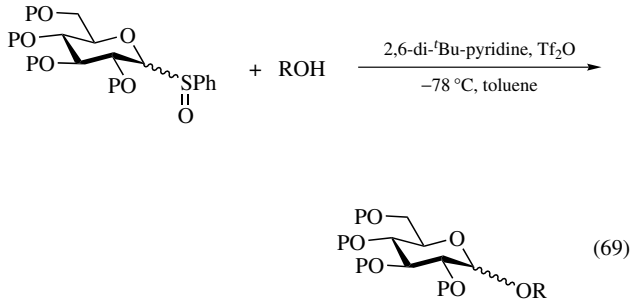
(67)

Owing to the electrophilicity of the divalent sulfur of a thiosulfinate, thiols do not react with Tf_2O to afford thiosulfonates; disulfides are obtained instead (eq 68).[101] In the presence of a base, only diphenyl disulfide is observed.[101]



(68)

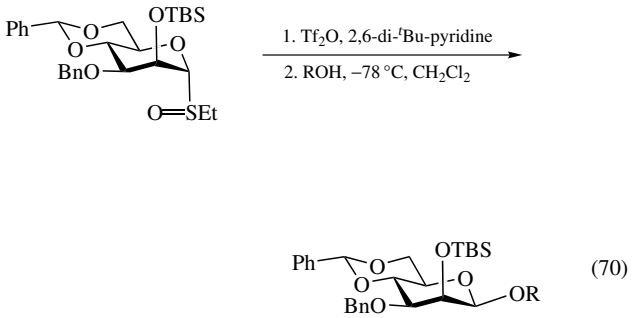
Glycosylations and Acetalations. The combination of Tf_2O and a hindered pyridine base such as 2,6-di-*tert*-butylpyridine promotes glycosylation of oxygen and nitrogen nucleophiles by thioglycoside sulfoxides.[102] This reaction has a broad scope, enabling the glycosylation of unreactive nucleophiles under mild conditions, and has been extended to solid phase glycosylations.[103] The anomeric stereochemistry of the product is determined by the nature of the protecting groups ('P'), with esters affording 1,2-*trans* products and ethers affording an anomeric stereochemistry that is sensitive to the reaction conditions (eq 69).[104]



(69)

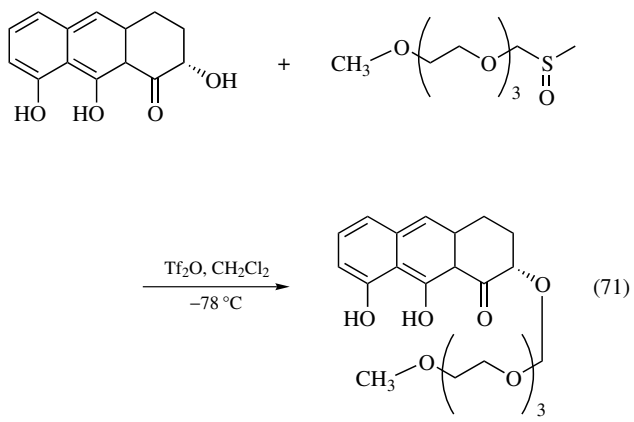
R = steroids, phenols, carbohydrates

An important modification of the original sulfoxide glycosylation uses 4,6-*O*-benzylidene-protected thioglycoside sulfoxides and a modified protocol for the addition of reagents, requiring the addition of the nucleophile after activation of the sulfoxide with Tf_2O.[105] This approach is effective in the production of the challenging β-manno 1,2-*cis*-glycosidic linkage, and there is strong evidence that the reaction proceeds via an intermediate glycosyl triflate (eq 70).[106,107]



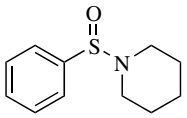
(70)

In some cases the addition of electrophilic alkenes, such as 4-allyl-1,2-dimethoxybenzene, to the reaction mixture can improve the outcome of the reaction, particularly when run in the presence of thioglycosides, by scavenging a by-product of the reaction, phenylsulfenyl triflate.[108] Non-carbohydrate thioacetal sulfoxides also undergo similar acetalation reactions when treated with Tf_2O (eq 71).[109]

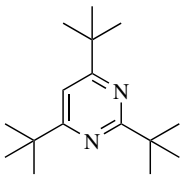


(71)

Thioglycosides can be activated towards glycosylation using a variety of reagents in combination with Tf_2O. In particular, the reagent combination of 1-benzenesulfinylpiperidine (BSP) (**9**), Tf_2O, and a hindered base, such as 2,6-di-*tert*-butylpyridine or 2,4,6-tri-*tert*-butylpyrimidine (TTBP) (**10**), is very effective.[110] The combination of BSP and TTBP is especially noteworthy as these reagents are crystalline and shelf-stable and may be stored premixed. The combination of diphenyl sulfoxide, Tf_2O, and TTBP has been shown to be a more powerful promoter than BSP/TTBP/Tf_2O for the activation of thioglycosides.[111] Again, for all of these reagent combinations, the use of 4,6-*O*-benzylidene acetals or 4,6-*O*-phenylboronates[112] enables the stereoselective formation of β-mannosides. The method has been used with moderate success on solid phase.[112] In the case of rhamnosides, where it is not possible to use a 4,6-*O*-benzylidene acetal, judicious choice of a 2-*O*-(3-trifluoromethylphenylsulfonyl) protecting group allows the preparation of the corresponding β-rhamnosides.[113]

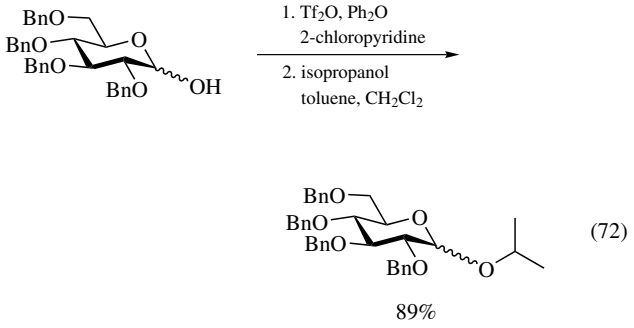


(9)



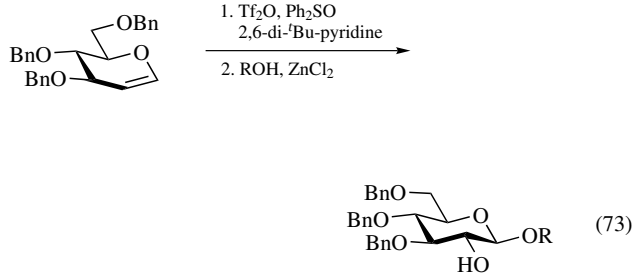
(10)

Tf_2O in combination with sulfoxides lacking α-protons, such as diphenylsulfoxide or dibenzothiophene sulfoxide, generates a sulfoxonium triflate, which is capable of effecting the formation of glycosides from carbohydrate hemiacetals and oxygen nucleophiles.[114] This is a dehydrative glycosylation, and appears to proceed by way of a sulfoxonium intermediate (eq 72).[115]



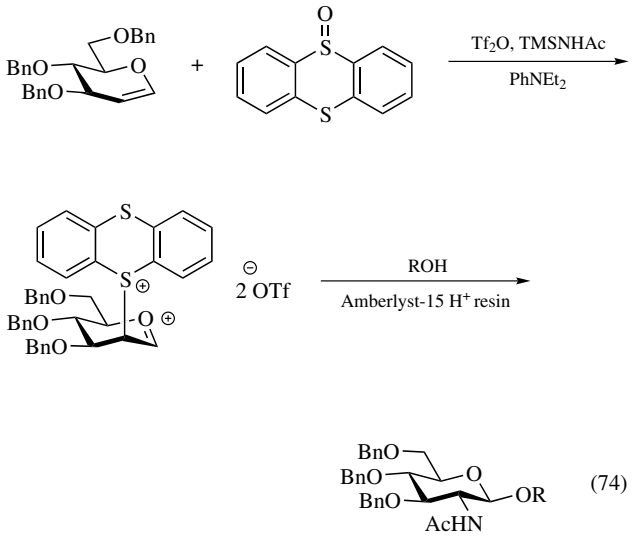
(72)

Carbohydrate glycals undergo oxidative glycosylation when treated first with Tf_2O and diphenyl sulfoxide (or tributylphosphine oxide)[116] and then with a nucleophile in the presence of a Lewis acid.[117] This reaction proceeds via oxygen transfer to generate a 1,2-anhydrosugar intermediate which is opened by nucleophiles in the presence of a Lewis acid, affording 2-hydroxy β-glucosides (eq 73). If a more hindered sulfoxide (dibenzothiophene sulfoxide) is used, the reaction occurs with the complimentary stereochemistry to give 2-hydroxy α-mannosides.[118]



(73)

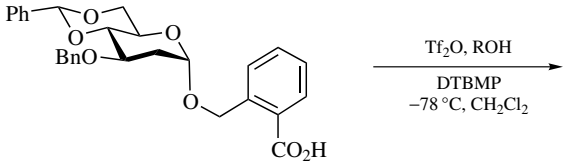
A variant of this reaction is termed as the C2-acetamidoglycosylation. Treatment of glycals with Tf_2O and thianthrene-5-oxide, followed by trimethylsilylacetamide and a base, and then finally with an alcohol nucleophile and an acid catalyst affords 2-acetamido glycosides (eq 74).[119]



(74)

R = carbohydrates, amino acids, and steroids

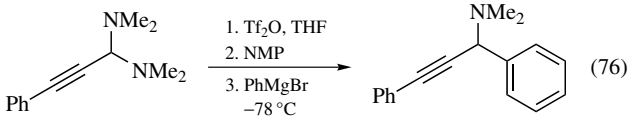
Tf_2O acts as a promoter in glycosylations of alcohols by 2′-carboxylbenzyl glycosides (eq 75).[120] This reaction most likely proceeds via the mixed anhydride.



(75)

Tf_2O has been used as a promoter in glycosylations of carbohydrate alcohols by glycosyl fluorides.[121]

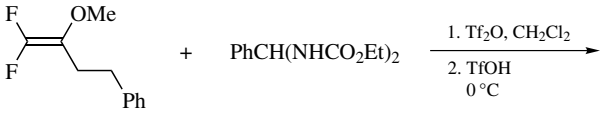
Aminals. Allylic and propargylic aminals when treated with Tf_2O afford iminium salts, which react with Grignard reagents to afford allylic and propargylic amines (eq 76).[122]

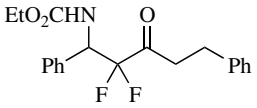


(76)

67%

1,1-Difluorovinyl methyl ethers and aminal bis(carbamates) or bis(sulfonamides) react in the presence of Tf_2O to generate β-amino-α,α-difluoroketones (eq 77).[123]

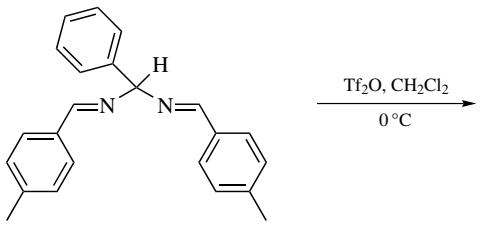


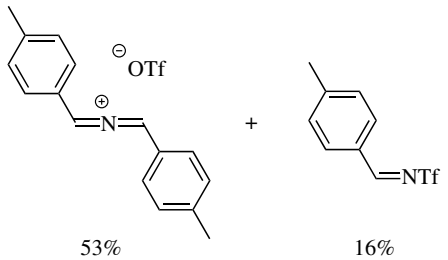


(77)

84%

An azaallenium salt has been prepared by treatment of a bis(iminomethane) compound with Tf_2O (eq 78).[124]

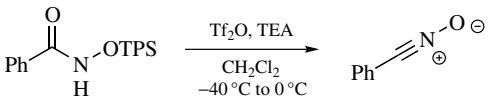


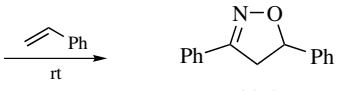


(78)

53% 16%

Other Applications. *O*-Silylated hydroxamic acids when treated with Tf_2O and a base yield nitrile oxides.[125] In the presence of olefins, these undergo [3 + 2] dipolar cycloadditions affording isoxazolines (eq 79).[125]

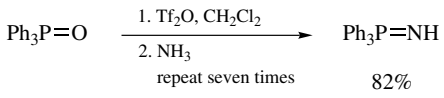




(79)

88%

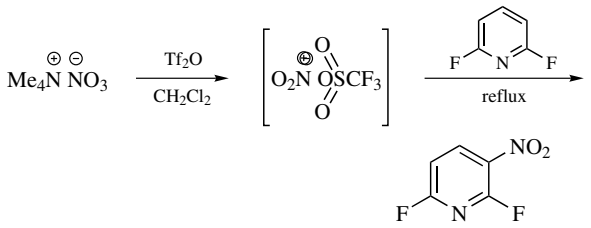
Triphenylphosphine oxide can be converted to the corresponding unsubstituted phosphinimines by repeated sequential treatment with Tf_2O and then ammonia (eq 80).[126]



(80)

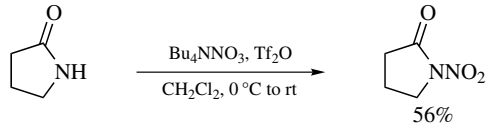
82%

The combination of tetraalkylammonium nitrates and Tf_2O generates nitronium triflate, which acts as a convenient anhydrous nitrating reagent.[127,128] This reagent system is effective for nitration of homo and heteroaromatic systems (eq 81),[127] and for *N*-nitration of saturated nitrogen heterocycles (eq 82).[128]



(81)

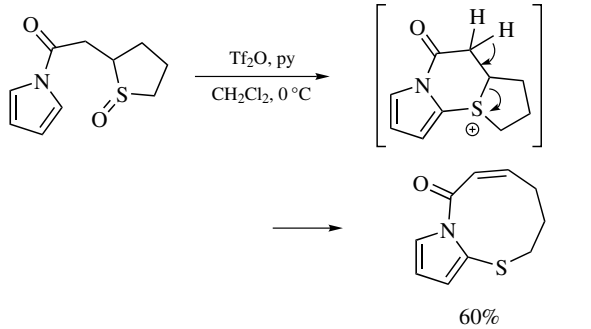
98%



(82)

56%

Treatment of sulfoxide-substituted electron-rich heterocycles with Tf_2O promotes substitution at sulfur, resulting in the formation of large-ring N,S-heterocycles (eq 83).[129]

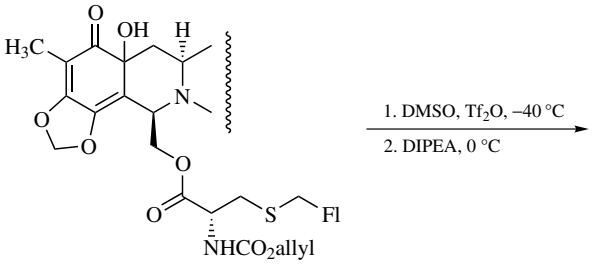


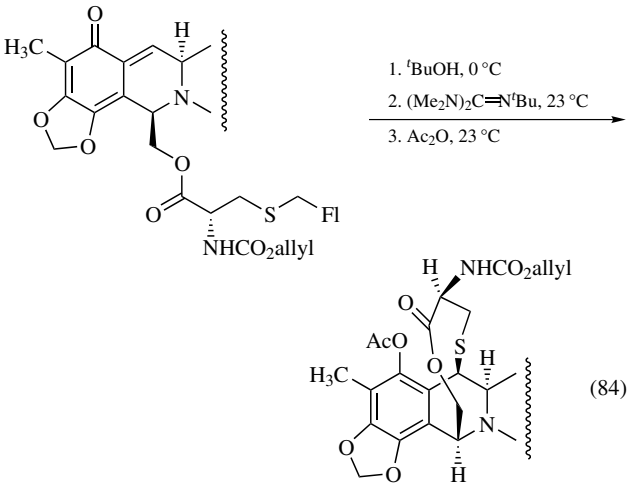
(83)

60%

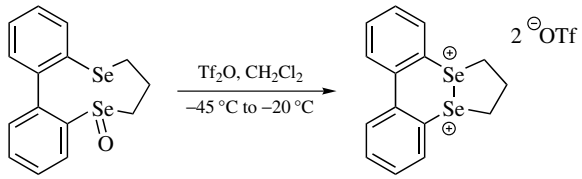
Dimethyl sulfide ditriflate, obtained from Tf_2O and DMSO, has been used to generate *o*-quinone methides (eq 84).[130]

Bis- and tris-chalcogen monoxides when treated with Tf_2O afford di- or tri-chalcogona dications, respectively; these salts can be considered 2-center, 2-electron or 3-center, 4-electron bonded species (eq 85).[131,132] These compounds are susceptible to nucleophilic attack at carbon or at the chalcogen and can act as alkylating agents under very mild conditions.[132]



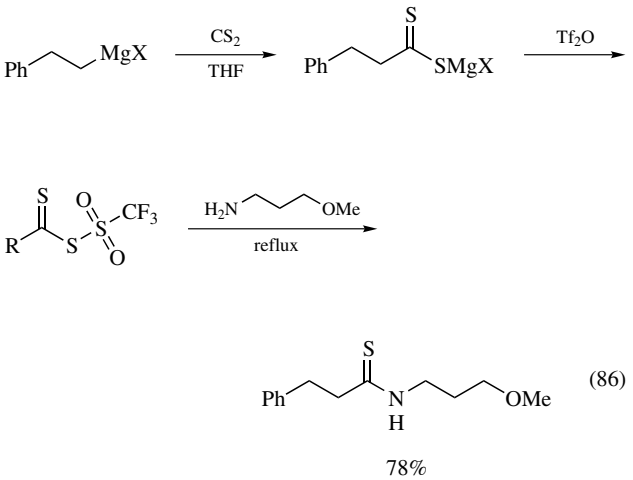


(84)



(85)

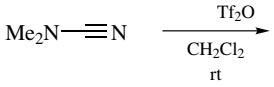
A one-pot procedure for the synthesis of thioamides relies on the successive reaction of Grignard reagents with carbon disulfide and then with Tf_2O to generate a mixed anhydride intermediate. This intermediate reacts with amines to generate thioamides (eq 86).[133]

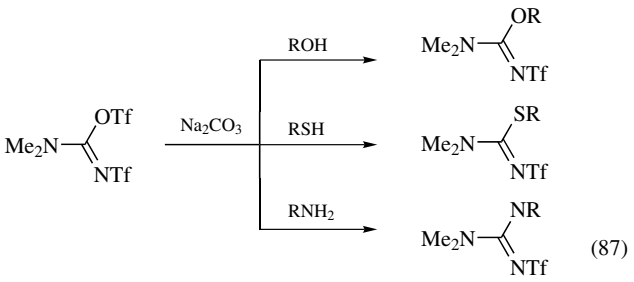


(86)

78%

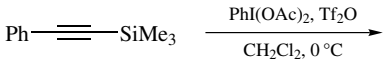
Tf_2O reacts with dimethylcyanamide to afford an *O*,*N*-ditriflylisourea.[134] Reaction of this isourea with alcohols, thiols, or amines affords isoureas, thioisoureas, or guanidines, respectively (eq 87).[134]

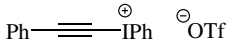




(87)

Trimethylsilylalkynes can be converted to alkynyl(phenyl) iodonium triflates by treatment with $PhI(OAc)_2$ and Tf_2O (eq 88).[135] Alkynyl(phenyl)iodonium triflates are useful 'electrophilic acetylene' equivalents and can act as Michael acceptors, 1,3-dipolariphiles and alkynyl cation equivalents.[136]

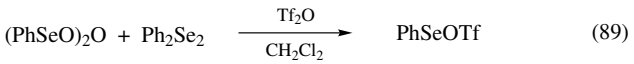




(88)

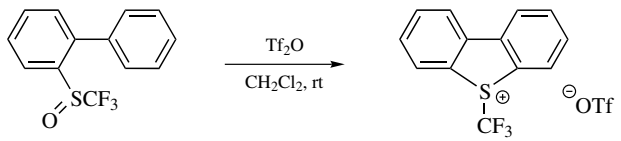
56%

The reaction of Tf_2O with phenylseleninic anhydride and diphenyl diselenide directly affords phenylselenenyl triflate (eq 89).[137] This procedure is a convenient alternative to the preparation of phenylselenenyl triflate from light sensitive AgOTf and moisture sensitive PhSeCl.

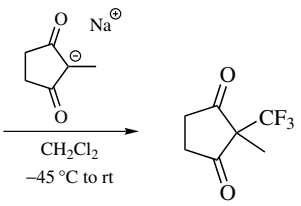


(89)

Electrophilic trifluoromethylation reagents can be generated from the treatment of trifluoromethyl biphenyl sulfoxides with Tf_2O.[138,139] These reagents will react with a wide range of nucleophiles including carbanions, aromatics, silyl enol ethers, thiolates, and phosphines (eq 90).[139]



75%



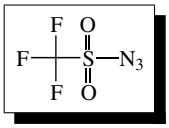
(90)

84%

1. (a) Gramstad, T.; Haszeldine, R. N., *J. Chem. Soc.* **1957**, 4069. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R., *Synthesis* **1982**, 85. (c) Stang, P. J.; White, M. R., *Aldrichim. Acta* **1983**, *16*, 15.
2. Binkley, R. W.; Ambrose, M. G., *J. Carbohydr. Chem.* **1984**, *3*, 1.
3. Ambrose, M. G.; Binkley, R. W., *J. Org. Chem.* **1983**, *48*, 674.
4. Stang, P. J.; Treptow, W., *Synthesis* **1980**, 283.
5. García Martínez, A.; Herrera Fernandez, A.; Martínez Alvarez, R.; Silva Losada, M. C.; Molero Vilchez, D.; Subramanian, L. R.; Hanack, M., *Synthesis* **1990**, 881.
6. Yoshida, M.; Takeuchi, K., *J. Org. Chem.* **1993**, *58*, 2566.
7. Jeanneret, V.; Gasparini, F.; Péchy, P.; Vogel, P., *Tetrahedron* **1992**, *48*, 10637.
8. Neenan, T. X.; Houlihan, F. M.; Reichmanis, E.; Kometani, J. M.; Bachman, B. J.; Thompson, L. F., *Macromolecules* **1990**, *23*, 145.
9. (a) Sato, K.; Hoshi, T.; Kajihara, Y., *Chem. Lett.* **1992**, 1469. (b) Izawa, T.; Nakayama, K.; Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T., *J. Chem. Soc., Perkin Trans. 1* **1992**, 3003. (c) Knapps, S.; Naughton, A. B. J.; Jaramillo, C.; Pipik, B., *J. Org. Chem.* **1992**, *57*, 7328.
10. Takeuchi, K.; Kitagawa, T.; Ohga, Y.; Yoshida, M.; Akiyama, F.; Tsugeno, A., *J. Org. Chem.* **1992**, *57*, 280.
11. Eaton, P. E.; Zhou, J. P., *J. Am. Chem. Soc.* **1992**, *114*, 3118.
12. Spitz, U. P., *J. Am. Chem. Soc.* **1993**, *115*, 10174.
13. Zheng, C. Y.; Slebocka-Tilk, H.; Nagorski, R. W.; Alvarado, L.; Brown, R. S., *J. Org. Chem.* **1993**, *58*, 2122.
14. Effenberger, F.; Weber, Th., *Chem. Ber.* **1988**, *121*, 421.
15. (a) Rubinsztajn, S.; Fife, W. K.; Zeldin, M., *Tetrahedron Lett.* **1992**, *33*, 1821. (b) Dodd, R. H.; Poissonnet, G.; Potier, P., *Heterocycles* **1989**, *29*, 365.
16. García Martínez, A.; Martínez Alvarez, R.; Teso Vilar, E.; García Fraile, A.; Hanack, M.; Subramanian, L. R., *Tetrahedron Lett.* **1989**, *30*, 581.
17. Sonoda, T.; García Martínez, A.; Hanack, M.; Subramanian, L. R., *Croat. Chim. Acta* **1992**, *65*, 585 (*Chem. Abstr.* **1993**, *118*, 168 491).
18. Ritter, K., *Synthesis* **1993**, 735.
19. Hendrickson, J. B.; Bergeron, R., *Tetrahedron Lett.* **1973**, 4607.
20. Hendrickson, J. B.; Bergeron, R.; Giga, A.; Sternbach, D. D., *J. Am. Chem. Soc.* **1973**, *95*, 3412.
21. Edwards, M. L.; Stemerick, D.; McCarthy, J. R., *Tetrahedron Lett.* **1990**, *31*, 3417.
22. Panetta, V.; Yaouanc, J. J.; Handel, H., *Tetrahedron Lett.* **1992**, *33*, 5505.
23. (a) McMurry, J. E.; Scott, W. J., *Tetrahedron Lett.* **1983**, *24*, 979. (b) Comins, J. E.; Dehghani, A., *Tetrahedron Lett.* **1992**, *33*, 6299. (c) Crisp, G. T.; Flynn, B. L., *Tetrahedron* **1993**, *49*, 5873.
24. Anders, E.; Stankowiak, A., *Synthesis* **1984**, 1039.
25. García Martínez, A.; Herrera Fernandez, A.; Alvarez, R. M.; Sánchez García, J. M., *An. Quim., Ser. C* **1981**, *77c*, 28 (*Chem. Abstr.* **1982**, *97*, 5840).
26. (a) Wright, M. E.; Pulley, S. R., *J. Org. Chem.* **1987**, *52*, 5036. (b) Dolle, R. E.; Schmidt, S. J.; Erhard, K. F.; Kruse, L. I., *J. Am. Chem. Soc.* **1989**, *111*, 278.
27. García Martínez, A.; Herrera Fernandez, A.; Moreno Jiménez, F.; García Fraile, A.; Subramanian, L. R.; Hanack, M., *J. Org. Chem.* **1992**, *57*, 1627.
28. Stang, P. J.; Kowalski, M. H.; Schiavelli, M. D.; Longford, R., *J. Am. Chem. Soc.* **1989**, *111*, 3347.
29. García Martínez, A.; Herrera Fernández, A.; Molero Vilchez, D.; Hanack, M.; Subramanian, L. R., *Synthesis* **1992**, 1053.
30. (a) Bentz, H.; Subramanian, L. R.; Hanack, M.; García Martínez, A.; Gómez Marin, M.; Perez-Ossorio, R., *Tetrahedron Lett.* **1977**, 9. (b) Kraus, W.; Zartner, G., *Tetrahedron Lett.* **1977**, 13. (c) García Martínez, A.; García Fraile, A.; Sánchez García, J. M., *Chem. Ber.* **1983**, *116*, 815. (d) García Martínez, A.; Teso Vilar, E.; Gómez Marin, M.; Ruano Franco, C., *Chem. Ber.* **1985**, *118*, 1282.
31. (a) García Martínez, A.; Teso Vilar, E.; López, J. C.; Manrique Alonso, J.; Hanack, M.; Subramanian, L. R., *Synthesis* **1991**, 353. (b) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Ruano Franco, C.; Soto Salvador, J.; Subramanian, L. R.; Hanack, M., *Synthesis* **1987**, 321.
32. (a) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Osío Barcina, J.; Hanack, M.; Subramanian, L. R., *Tetrahedron Lett.* **1989**, *30*, 1503. (b) García Martínez, A.; Teso Vilar, E.; Osío Barcina, J.; Manrique Alonso, J.; Rodríguez Herrero, E.; Hanack, M.; Subramanian, L. R., *Tetrahedron Lett.* **1992**, *33*, 607.
33. García Martínez, A.; Herrera Fernandez, A.; Sánchez García, J. M., *An. Quim.* **1979**, *75*, 723 (*Chem. Abstr.* **1980**, *93*, 45 725).
34. García Martínez, A.; Espada Rios, I.; Osío Barcina, J.; Teso Vilar, E., *An. Quim., Ser. C* **1982**, *78c*, 299 (*Chem. Abstr.* **1983**, *98*, 159 896).
35. (a) García Martínez, A.; Espada Rios, I.; Teso Vilar, E., *Synthesis* **1979**, 382. (b) García Martínez, A.; Espada Rios, I.; Osío Barcina, J.; Montero Hernando, M., *Chem. Ber.* **1984**, *117*, 982.
36. Hanack, M.; Hassdenteufel, J. R., *Chem. Ber.* **1982**, *115*, 764.
37. Stang, P. J.; Maas, G.; Smith, D. L.; McCloskey, J. A., *J. Am. Chem. Soc.* **1981**, *103*, 4837.
38. Wittmann, H.; Ziegler, E.; Sterk, H., *Monatsh. Chem.* **1987**, *118*, 531.
39. Wright, M. E.; Pulley, S. R., *J. Org. Chem.* **1989**, *54*, 2886.
40. García Martínez, A.; Martínez Alvarez, R.; García Fraile, A.; Subramanian, L. R.; Hanack, M., *Synthesis* **1987**, 49.
41. Stang, P. J., *Chem. Rev.* **1978**, *78*, 383.
42. García Martínez, A.; Herrera Fernandez, A.; Martínez Alvarez, R.; García Fraile, A.; Calderón Bueno, J.; Osío Barcina, J.; Hanack, M.; Subramanian, L. R., *Synthesis* **1986**, 1076.
43. García Martínez, A.; Osío Barcina, J.; Rys, A. Z.; Subramanian, L. R., *Tetrahedron Lett.* **1992**, *33*, 7787.
44. García Martínez, A.; Martínez Alvarez, R.; Martínez Gonzalez, S.; Subramanian, L. R.; Conrad, M., *Tetrahedron Lett.* **1992**, *33*, 2043.
45. García Martínez, A.; Martínez Alvarez, R.; Madueño Casado, M.; Subramanian, L. R.; Hanack, M., *Tetrahedron* **1987**, *43*, 275.
46. Negishi, E.; Owczarczyk, Z.; Swanson, D. R., *Tetrahedron Lett.* **1991**, *32*, 4453.
47. Evans, D. A.; Sjogren, E. B., *Tetrahedron Lett.* **1985**, *26*, 3787.
48. (a) Houpis, I. N., *Tetrahedron Lett.* **1991**, *32*, 6675. (b) Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald III, J. H.; Munroe, J. E., *J. Org. Chem.* **1989**, *54*, 5828.
49. (a) Effenberger, F.; Sohn, E.; Epple, G., *Ber. Dtsch. Chem. Ges./Chem. Ber.* **1983**, *116*, 1195. (b) Effenberger, F., *Angew. Chem.* **1980**, *92*, 147; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 151.
50. García Martínez, A.; Herrera Fernández, A.; Molero Vilchez, D.; Laorden Gutiérrez, L.; Subramanian, L. R., *Synlett* **1993**, 229.
51. Robl, J. A., *Synthesis* **1991**, 56.
52. Falmagne, J.-B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L., *Angew. Chem.* **1981**, *93*, 926; *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879.
53. García Martínez, A.; Martínez Alvarez, R.; Osío Barcina, J.; de la Moya Cerero, S.; Teso Vilar, E.; García Fraile, A.; Hanack, M.; Subramanian, L. R., *J. Chem. Soc., Chem. Commun.* **1990**, 1571.
54. Gramstad, T.; Husebye, S.; Saebo, J., *Tetrahedron Lett.* **1983**, *24*, 3919.
55. Thomas, E. W., *Synthesis* **1993**, 767.
56. Hendrickson, J. B.; Bair, K. W., *J. Org. Chem.* **1977**, *42*, 3875.
57. Hendrickson, J. B.; Schwartzman, S. M., *Tetrahedron Lett.* **1975**, 277.
58. Hendrickson, J. B.; Schwartzman, S. M., *Tetrahedron Lett.* **1975**, 273.
59. Lindner, E.; v. Au, G.; Eberle, H.-J., *Chem. Ber.* **1981**, *114*, 810.
60. Maas, G.; Lorenz, W., *J. Org. Chem.* **1984**, *49*, 2273.
61. (a) Stang, P. J.; Magnum, M. G.; Fox, D. P.; Haak, P., *J. Am. Chem. Soc.* **1974**, *96*, 4562. (b) Hanack, M.; Märkl, R.; García Martínez, A., *Chem. Ber.* **1982**, *115*, 772.
62. (a) Kitamura, T.; Furuki, R.; Nagata, K.; Taniguchi, H.; Stang, P. J., *J. Org. Chem.* **1992**, *57*, 6810. (b) Stang, P. J.; Zhdankin, V. V.; Tykwinski, R.; Zefirov, N., *Tetrahedron Lett.* **1992**, *33*, 1419.

63. Raghavan, S.; Kahne, D., *J. Am. Chem. Soc.* **1993**, *115*, 1580.
64. Taylor, S. L.; Martin, J. C., *J. Org. Chem.* **1987**, *52*, 4147.
65. Baldwin, J. E.; O'Neil, I. A., *Synlett* **1990**, 603.
66. Singer, B.; Maas, G., *Chem. Ber.* **1987**, *120*, 485.
67. Netscher, T.; Bohrer, P., *Tetrahedron Lett.* **1996**, *37*, 8359.
68. Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S., *Tetrahedron* **2000**, *56*, 3077.
69. Ross, A. S.; Pitie, M.; Meunier, B., *J. Chem. Soc., Perkin Trans. 1* **2000**, 571.
70. Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H., *Org. Lett.* **2002**, *4*, 4717.
71. Binkley, R. W.; Ambrose, M. G., *J. Org. Chem.* **1983**, *48*, 1776.
72. Martin, O. R.; Yang, F.; Xie, F., *Tetrahedron Lett.* **1995**, *36*, 47.
73. Yang, B.-H.; Jiang, J.-Q.; Ma, K.; Wu, H.-M., *Tetrahedron Lett.* **1995**, *36*, 2831.
74. Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K., *Synlett* **1995**, 739.
75. Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B., *Chem. Rev.* **2003**, *103*, 977.
76. Suzuki, H.; Kuroda, C., *Tetrahedron* **2003**, *59*, 3157.
77. Jonas, S.; Westerhausen, M.; Simchen, G., *J. Organometallic Chem.* **1997**, *548*, 131.
78. Simchen, G.; Jonas, S., *J. Prakt. Chem.* **1998**, *340*, 506.
79. Nishiyama, T.; Ono, Y.; Kurokawa, S.; Kimura, S., *Chem. Pharm. Bull.* **2000**, *48*, 1999.
80. Katritzky, A. R.; Zhang, S.; Fang, Y., *Org. Lett.* **2000**, *2*, 3789.
81. Martinez, A. G.; Vilar, E. T.; Jimenez, F. M.; Bilbao, C. M., *Tetrahedron: Asymmetry* **1997**, *8*, 3031.
82. Martinez, A. G.; Fernandez, A. H.; Moreno-Jimenez, F.; Fraile, M. J. L.; Subramanian, L. R., *Synlett* **1994**, 559.
83. Martinez, A. G.; Fernandez, A. H.; Alvarez, R. M.; Vilchez, M. D. M.; Gutierrez, M. L. L.; Subramanian, L. R., *Tetrahedron* **1999**, *55*, 4825.
84. Herrera, A.; Martinez-Alvarez, R.; Ramiro, P.; Chioua, M.; Torres, R., *Tetrahedron* **2002**, *58*, 3755.
85. Sforza, S.; Dossena, A.; Corradini, R.; Virgili, E.; Marchelli, R., *Tetrahedron Lett.* **1998**, *39*, 711.
86. Charette, A. B.; Grenon, M., *Tetrahedron Lett.* **2000**, *41*, 1677.
87. Alder, R. W.; Blake, M. E.; Bufali, S.; Butts, C. P.; Orpen, A. G.; Schutz, J.; Williams, S. J., *J. Chem. Soc., Perkin Trans. 1* **2001**, 1586.
88. Charette, A. B.; Chua, P., *Synlett* **1998**, 163.
89. Charette, A. B.; Chua, P., *Tetrahedron Lett.* **1998**, *39*, 245.
90. Charette, A. B.; Chua, P., *J. Org. Chem.* **1998**, *63*, 908.
91. Charette, A. B.; Chua, P., *Tetrahedron Lett.* **1997**, *38*, 8499.
92. Vonhoff, S.; Vasella, A., *Synth. Commun.* **1999**, *29*, 551.
93. McDonald, C. E.; Galka, A. M.; Green, A. I.; Keane, J. M.; Kowalchick, J. E.; Micklitsch, C. M.; Wisnoski, D. D., *Tetrahedron Lett.* **2001**, *42*, 163.
94. Liras, S.; Allen, M. P.; Segelstein, B. E., *Synth. Commun.* **2000**, *30*, 437.
95. Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M., *J. Org. Chem.* **2003**, *68*, 2609.
96. Black, D. S. C.; Rezaie, R., *Tetrahedron Lett.* **1999**, *40*, 4251.
97. Bose, D. S.; Jayalakshmi, B., *Synthesis* **1999**, 64.
98. Nenajdenko, V. G.; Vertelezkij, P. V.; Koldobskij, A. B.; Alabugin, I. V.; Balenkova, E. S., *J. Org. Chem.* **1997**, *62*, 2483.
99. Nishiyama, T.; Seshita, T.; Shodai, H.; Aoki, K.; Kameyama, H.; Komura, K., *Chem. Lett.* **1996**, 549.
100. Eschwey, M.; Sundermeyer, W.; Stephenson, D. S., *Chem. Ber.* **1983**, *116*, 1623.
101. Billard, T.; Langlois, B. R.; Large, S.; Anker, D.; Roidot, N.; Roure, P., *J. Org. Chem.* **1996**, *61*, 7545.
102. Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D., *J. Am. Chem. Soc.* **1989**, *111*, 6881.
103. Liang, R.; Yan, L.; Loebach, J.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W. C.; Kahne, D., *Science* **1996**, *274*, 1520.
104. Yan, L.; Kahne, D., *J. Am. Chem. Soc.* **1996**, *118*, 9239.
105. Crich, D.; Sun, S., *J. Org. Chem.* **1997**, *62*, 1198.
106. Crich, D.; Sun, S., *J. Am. Chem. Soc.* **1997**, *119*, 11217.
107. Crich, D., *J. Carbohydr. Chem.* **2002**, *21*, 667.
108. Gildersleeve, J.; Smith, A.; Sakurai, K.; Raghavan, S.; Kahne, D., *J. Am. Chem. Soc.* **1999**, *121*, 6176.
109. Silva, D. J.; Kahne, D.; Kraml, C. M., *J. Am. Chem. Soc.* **1994**, *116*, 2641.
110. Crich, D.; Smith, M., *J. Am. Chem. Soc.* **2001**, *123*, 9015.
111. Codee, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A., *Org. Lett.* **2003**, *5*, 1519.
112. Crich, D.; Smith, M., *J. Am. Chem. Soc.* **2002**, *124*, 8867.
113. Crich, D.; Picione, J., *Org. Lett.* **2003**, *5*, 781.
114. Gin, D., *J. Carbohydr. Chem.* **2002**, *21*, 645.
115. Garcia, B. A.; Poole, J. L.; Gin, D. Y., *J. Am. Chem. Soc.* **1997**, *119*, 7597.
116. Mukaiyama, T.; Suda, S., *Chem. Lett.* **1990**, 1143.
117. Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y., *J. Am. Chem. Soc.* **1998**, *120*, 13515.
118. Kim, J.-Y.; Di Bussolo, V.; Gin, D. Y., *Org. Lett.* **2001**, *3*, 303.
119. Liu, J.; Gin, D. Y., *J. Am. Chem. Soc.* **2002**, *124*, 9789.
120. Kim, K. S.; Park, J.; Lee, Y. J.; Seo, Y. S., *Angew. Chem., Int. Ed.* **2003**, *42*, 459.
121. Toshima, K., *Carbohydr. Res.* **2000**, *327*, 15.
122. Gommermann, N.; Koradin, C.; Knochel, P., *Synthesis* **2002**, 2143.
123. Kodama, Y.; Okumura, M.; Yanabu, N.; Taguchi, T., *Tetrahedron Lett.* **1996**, *37*, 1061.
124. Bottger, G.; Geisler, A.; Frohlich, R.; Wurthwein, E.-U., *J. Org. Chem.* **1997**, *62*, 6407.
125. Muri, D.; Bode, J. W.; Carreira, E. M., *Org. Lett.* **2000**, *2*, 539.
126. Hendrickson, J. B.; Sommer, T. J.; Singer, M., *Synthesis* **1995**, 1496.
127. Shackelford, S. A.; Anderson, M. B.; Christie, L. C.; Goetzen, T.; Guzman, M. C.; Hananel, M. A.; Kornreich, W. D.; Li, H.; Pathak, V. P.; Rabinovich, A. K.; Rajapakse, R. J.; Truesdale, L. K.; Tsank, S. M.; Vazir, H. N., *J. Org. Chem.* **2003**, *68*, 267.
128. Adams, C. M.; Sharts, C. M.; Shackelford, S. A., *Tetrahedron Lett.* **1993**, *34*, 6669.
129. Bates, D. K.; Xia, M., *J. Org. Chem.* **1998**, *63*, 9190.
130. Corey, E. J.; Gin, D. Y.; Kania, R. S., *J. Am. Chem. Soc.* **1996**, *118*, 9202.
131. Furukawa, N.; Kobayashi, K.; Sato, S., *J. Organometallic Chem.* **2000**, *611*, 116.
132. Nenajdenko, V. G.; Shevchenko, N. E.; Balenkova, E. S.; Alabugin, I. V., *Chem. Rev.* **2003**, *103*, 229.
133. Katritzky, A. R.; Moutou, J.-L.; Yang, Z., *Synthesis* **1995**, 1497.
134. Martinez, A. G.; Fernandez, A. H.; Jimenez, F. M.; Ruiz, P. M.; Subramanian, L. R., *Synlett* **1995**, 161.
135. Kitamura, T.; Kotani, M.; Fujiwara, Y., *Synthesis* **1998**, 1416.
136. Stang, P. J.; Zhdankin, V. V., *Chem. Rev.* **1996**, *96*, 1123.
137. Kutateladze, A. G.; Kice, J. L.; Kutateladze, T. G.; Zefirov, N. S.; Zyk, N. V., *Tetrahedron Lett.* **1992**, *33*, 1949.
138. Umemoto, T.; Ishihara, S., *Tetrahedron Lett.* **1990**, *31*, 3579.
139. Umemoto, T.; Ishihara, S., *J. Am. Chem. Soc.* **1993**, *115*, 2156.

Trifluoromethanesulfonyl Azide



[3855-45-6] $CF_3N_3O_2S$ (MW 175.09)
InChI = 1/CF3N3O2S/c2-1(3,4)10(8,9)7-6-5
InChIKey = NQPHMXWPDCSHTE-UHFFFAOYAT

(reagent for diazo or trifluoromethanesulfonylamino transfer)

Alternate Name: triflyl azide, TfN_3.

Physical Data: colorless liquid with a pungent odor, bp 80–81 °C,[7] 52.3 °C (444 mm Hg),[1] 45 °C (350 mm Hg),[3] n_D^{20} 1.3474,[7] d_4^{20} 1.5400.[7]

Solubility: soluble in most organic solvents, e.g. hexane, decalin, dichloromethane, THF, dioxane, acetone, MeCN, DMF, DMSO, MeOH.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: IR,[1–6] Raman,[6] ^{19}F-NMR,[2] MS,[3] UV;[1,7] other analysis: gas electron diffraction.[8]

Preparative Methods: from Tf_2O and NaN_3 in H_2O/CH_2Cl_2,[2,5] Tf_2O and NaN_3 in H_2O/catalyst Bu_4NHSO_4/hexane,[4] TfF and NaN_3 in MeOH,[7] or TfCl and NaN_3 in MeCN.[3]

Purification: distillation at reduced pressure[1,3] (CAUTION!).

Handling, Storage, and Precautions: prepared in situ as a solution in dichloromethane,[5] hexane,[4] MeCN,[3] or $ClCH_2CH_2Cl$.[9] Solutions in dichloromethane are stable at −14 °C for several weeks;[10] solutions in hexane are stable at 4 °C for several days.[4] Neat TfN_3 is stable up to 100 °C.[7]

CAUTION: Preparation of TfN_3 in the absence of an organic solvent should be avoided as it may lead to an explosion.[2] Reactions involving neat TfN_3 should always be handled behind a safety shield.

Original Commentary

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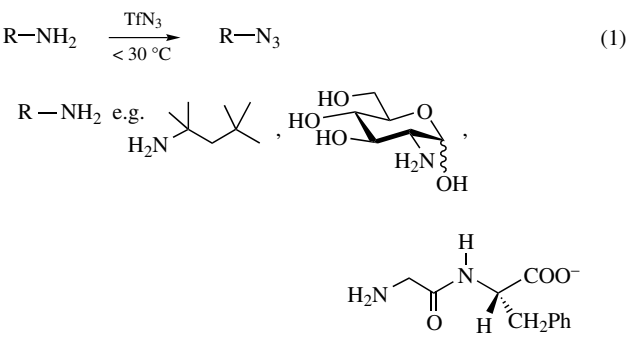
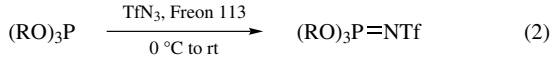
ETH-Zurich, ETH-Hoenggerberg, Zurich, Switzerland

Introduction. TfN_3 acts both as diazo- and as triflylamino-transfer reagent. Unlike other sulfonyl azides, it does not act as azido-transfer reagent, but readily undergoes cycloaddition to electron-rich alkenes at room temperature.

Transformation of Primary Amines into Azides. Azido groups are equivalents of temporarily protected primary amino groups. TfN_3 transforms primary amines into azides in a single step (eq 1). The reaction has been applied to alkylamines,[2] aminodeoxyhexoses,[5,11] amino acids, and peptides.[12] The reaction is base catalysed. The reaction conditions are strongly influenced by the polarity of the amines. Lutidine in dichloromethane has been used for the azidation of lipophilic amines, DMAP in $MeCN/CH_2Cl_2$ or in $MeOH/CH_2Cl_2$, or NaOH (pH = 9.5) in H_2O/CH_2Cl_2 for hydrophilic amines. Yields vary from 19% to 93%.

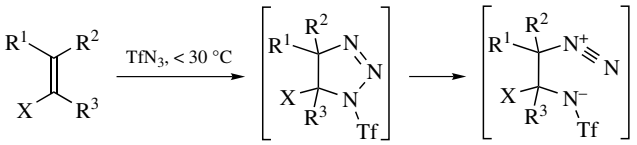


Imination of Phosphites and Phenylphosphonous Dihalides. TfN_3 reacts with $(PhO)_3P$ and $(C_6H_{13}O)_3P$ quantitatively to *N*-triflyl-phosphorimidates[13] (eq 2). Similarly, $PhPX_2$ (X = F, Cl, or Br) afford the corresponding phosphonimidic dihalides, whereas phosphorous trihalides do not react.

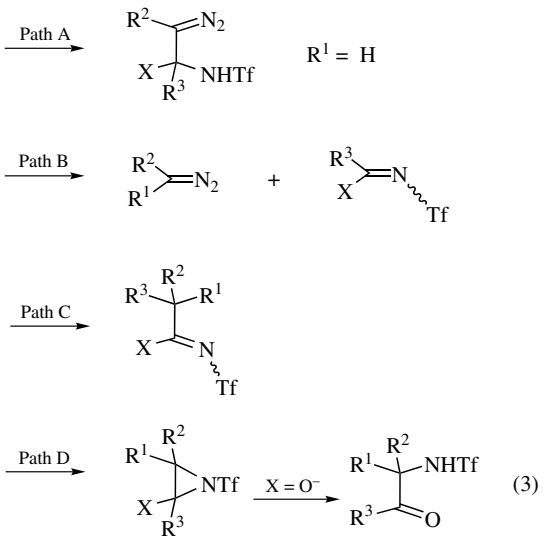


R = Ph or C_6H_{13}

1,3-Dipolar Cycloaddition to Electron-rich Alkenes. At temperatures less than 30 °C, TfN_3 adds to enolates,[10] enol ethers,[4,14] and enamines[9,15,16] to form thermally unstable 1,2,3-triazolines which ring open to give unstable diazonium-triflylamide zwitterions (eq 3). Depending on the nature of R^1 to R^3 and X, these zwitterions form a variety of products.

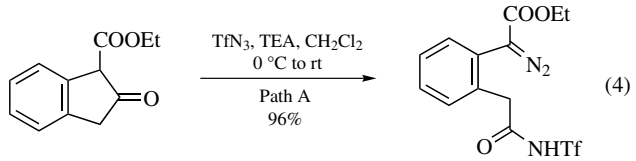


X = RO, O^-, R_2N



The aryldiazoacetate obtained via path A from ethyl indan-1-one-2-carboxylate is stable enough to be isolated (eq 4), whereas the diazo group of the benzyldiazoacetate derived from the isomeric ethyl indan-2-one-1-carboxylate reacts in situ with the

N-triflylamido group to yield bicyclic products.[10] Acyclic β-keto esters react with TfN_3 via path B to give diazo esters (eq 5). Ethyl α-tetralone-2-carboxylate and benzosuberone-2-carboxylate yield the ring-contracted *N*-triflylamides via path C (eq 6), whereas ethyl β-tetralone-1-carboxylate is transformed via path D to a *N*-triflylamine without ring contraction (eq 7).



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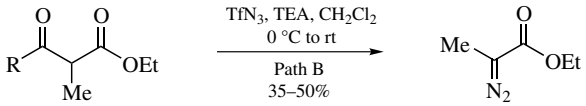
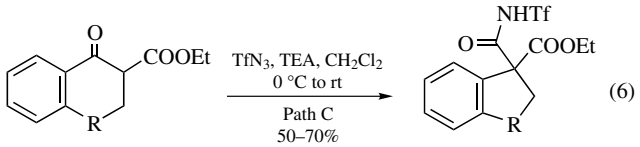


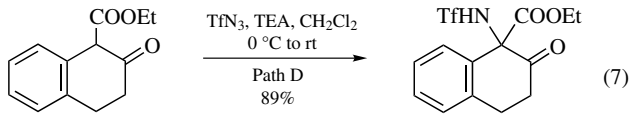
(5)

R = Me or Ph



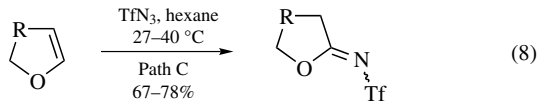
(6)

R = CH_2 or CH_2CH_2



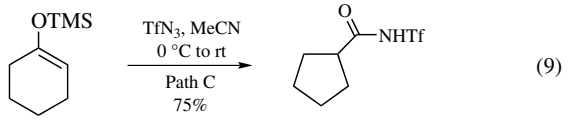
(7)

2,3-Dihydrofuran and 3,4-dihydro-2*H*-pyran react with TfN_3 to afford *N*-triflylimino ethers (i.e. lactone *N*-triflylimines)[4] (eq 8), whereas cyclohex-1-enol TMS ether is transformed into a triflylamide[14] (eq 9). These reactions occur via path C, in the former case by a hydride shift and in the latter case by an alkyl shift leading to ring contraction. Open-chain silyl enol ethers, however, react via path D to *N*-triflyl α-amino ketones[14] (eq 10). The yield drops to 28% upon replacement of the *tert*-butyl by a phenyl group.



(8)

R = CH_2 or CH_2CH_2



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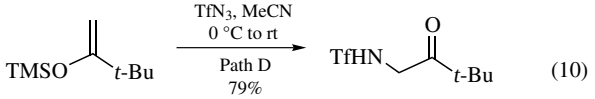
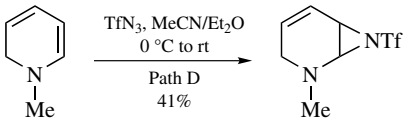
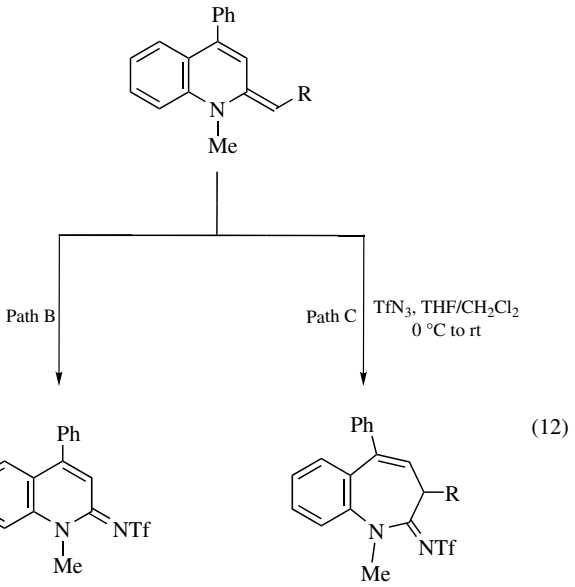


(10)

The reaction of TfN_3 with 1-methyl-1,2-dihydropyridine gave the triflylaziridine via path D[15] (eq 11). In situ generated 1,2-dihydro-1-methyl-2-alkylidenequinolines react with TfN_3 to *N*-triflylamidines, either via path C by alkenyl migration and ring enlargement, or via path B by fragmentation[16] (eq 12). Partial hydrolysis of the quinoline derivative led to the corresponding δ-lactam (<15%). The relative extent of the fragmentation increases with increasing stability of $RCHN_2$ (Me < *t*-Bu < Ph).



(11)



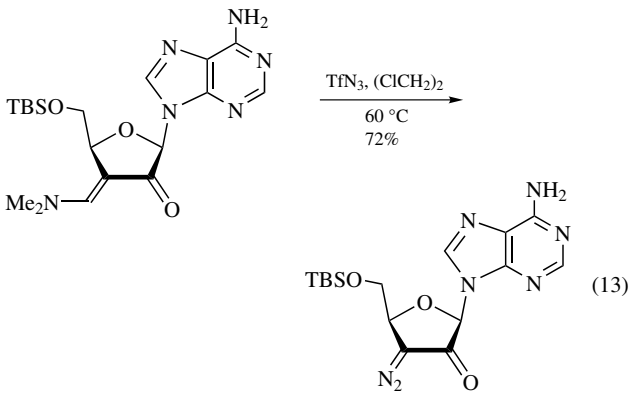
(12)

\+ $RCHN_2$ (not isolated)

Via path B and path C

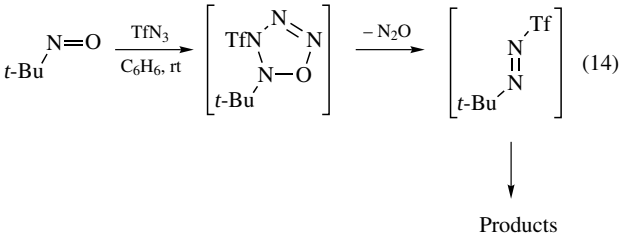
R = Me	8%	74%
R = *t*-Bu	17%	51%
R = Ph	82%	13%
R = H	7%	–

The decomposition of the 1,2,3-triazoline intermediate via path B is also favored by the presence of a keto group, and leads to an α-diazo ketone. α-Diazo ketones are thus available from α-methylene ketones in two steps [1. $(MeO)_2CHNMe_2$; 2. TfN_3, 60 °C] and under mild conditions[9] (the key step is shown in eq 13).



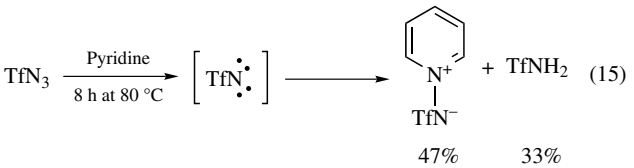
(13)

1,3-Dipolar Cycloaddition to Nitroso Compounds. The addition of TfN_3 to 2-nitroso-2-methyl-propane leads to a thermally unstable oxatetrazolidine which loses N_2O to afford TfN = N-*t*-Bu[17] (eq 14). This cycloaddition has not been used for synthetic purposes, although TfN = N-*t*-Bu homolytically decomposes to CF_3 and *tert*-butyl radicals.

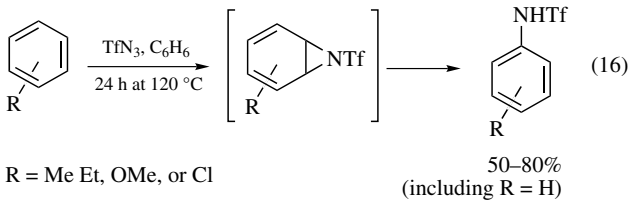


(14)

Triflyl Nitrene Addition to Pyridine and Benzenes. At higher temperature (>ca. 80 °C), TfN_3 slowly decomposes to triflyl nitrene which adds to pyridine to form pyridinium *N*-triflylaminide[18] (eq 15). Triflyl nitrene also adds to benzene to form *N*-triflylaniline, and to monosubstituted benzenes to form mostly *ortho*/*para* disubstituted *N*-triflylanilines in ratios between 1:1 and 2:1)[3] (eq 16).



(15)



(16)

First Update

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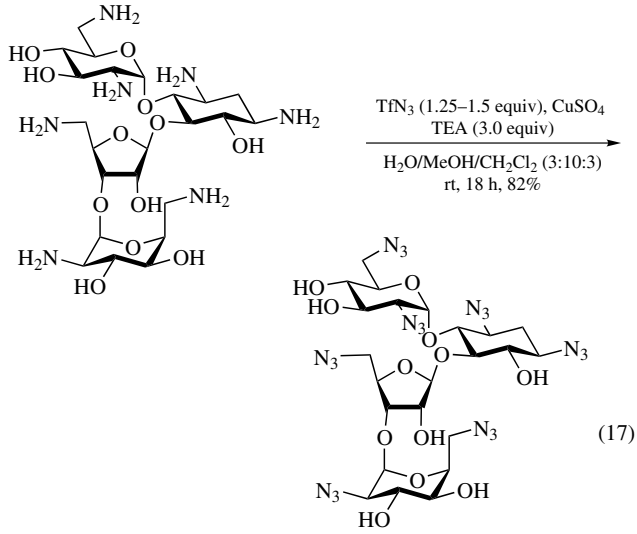
Gilead Sciences, Foster City, CA, USA

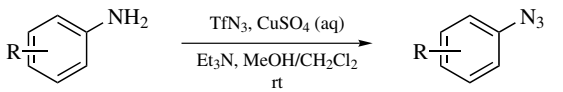
Yitzhak Tor
University of California, San Diego, CA, USA

Transformation of Primary Amines into Azides. Since its introduction by Ruff in 1965,[1] TfN_3 has been widely used as a diazo transfer reagent that converts primary amines into azides. Recently, Wong further popularized this reaction with addition of various metal catalysts (e.g., Cu^{2+}, Zn^{2+}, and Ni^{2+}), which dramatically increase the efficiency of this transformation with shortened reaction times.[19] Neomycin, for example, with six primary amino groups, can be converted to its per-azido counterpart in 82% yield using $CuSO_4$ as a catalyst (eq 17). The same reaction proceeds in merely 20% yield in the absence of catalysts under the same conditions.[20]

The conditions developed by Wong can also be applied to transform aromatic amines into the corresponding azides (eq 18).[21] The yields of the reactions generally depend on the nucleophilicity of the amine. Electron-rich as well as sterically demanding anilines react effectively while electron-withdrawing groups retard the process. Notably, the mild conditions allow for smooth conversion in the presence of acid-labile functional groups (e.g., Boc) where traditional diazotization would have failed.



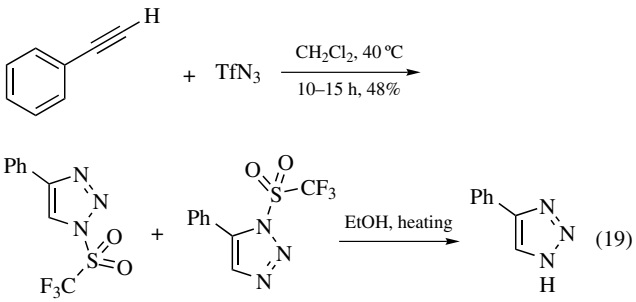
(17)



(18)

R	Reaction time	Yield
4-OMe	0.6 h	90%
2,6-Diisopropyl	1.5 h	92%
4-COOH	3.0 h	88%
4-CH_2NHBoc	1.5 h	96%
4-CN	24 h	7%

1,3-Dipolar Cycloaddition to Alkynes.[22] TfN_3 reacts with phenylacetylene in methylene chloride to give rise to a mixture of 1,3-cycloaddition products that, upon heating in ethanol, result in transformation into 4-phenyl-1*H*-1,2,3-triazole by releasing CH_3SO_2OEt (eq 19). When heating TfN_3 and phenylacetylene in ethanol, 4-phenyl-1*H*-1,2,3-triazole is generated in 50% yield (eq 20). This reaction provides a convenient method to access substituted 1*H*-1,2,3-triazoles.



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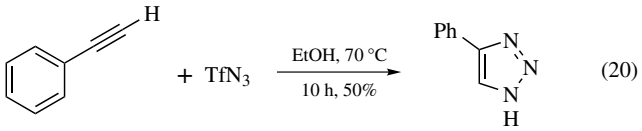
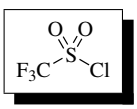


(20)

Related Reagents. $C_6F_{13}SO_2N_3$; $C_8F_{17}SO_2N_3$; $XC_2F_4OC_2F_4SO_2N_3$ (X = H, Cl, I); FSO_2N_3, MsN_3, $PhSO_2N_3$, TsN_3; $ClC_6H_4SO_2N_3$, $MeOC_6H_4SO_2N_3$; $O_2NC_6H_4SO_2N_3$; Trisyl Azide; PhN_3.

1. Ruff, J. K., *Inorg. Chem.* **1965**, *4*, 567.
2. Cavender, C. J.; Shiner, V. J., Jr., *J. Org. Chem.* **1972**, *37*, 3567.
3. Kamigata, N.; Yamamoto, K.; Kawakita, O.; Hikita, K.; Matsuyama, H.; Yoshida, M.; Kobayashi, M., *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3601.
4. Fritschi, S.; Vasella, A., *Helv. Chim. Acta* **1991**, *74*, 2024.
5. Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M., *Helv. Chim. Acta* **1991**, *74* 2073.
6. Alvarez, R. M. S.; Cutin, E. H.; Romano, R. M.; Mack, H.-G.; Della Vedova, C. O., *Spectrochim. Acta, Part A, Molec. Biomolec. Spectrosc.* **1998**, *54*, 605.
7. Nazaretyan, V. P.; Yagupol'skii, L. M., *J. Org. Chem. USSR* **1978**, *14*, 192.
8. Haist, R.; Mack, H. G.; Della Vedova, C. O.; Cutin, E. H.; Oberhammer, H., *J. Mol. Struct.* **1998**, *445*, 197.
9. Norbeck, D. W.; Kramer, J. B., *J. Am. Chem. Soc.* **1988**, *110*, 7217.
10. Benati, L.; Nanni, D.; Spagnolo, P., *J. Org. Chem.* **1999**, *64*, 5132.
11. Ludin, C.; Schwesinger, B.; Schwesinger, R.; Meier, W.; Seitz, B.; Weller, T.; Hoenke, C.; Haitz, S.; Erbeck, S.; Prinzbach, H., *J. Chem. Soc., Perkin Trans. 1* **1994**, 2685.
12. Zaloom, J.; Roberts, D. C., *J. Org. Chem.* **1981**, *46*, 5173.
13. Radchenko, O. A.; Nazaretyan, V. P.; Yagupol'skii, L. M., *J. Gen. Chem. USSR* **1976**, *46*, 561.
14. Xu, Y.; Xu, G.; Zhu, S.; Zhu, G.; Jia, Y.; Huang, Q., *J. Fluorine Chem.* **1999**, *96*, 79.
15. Ondrus, T. A.; Pednekar, P. R.; Knaus, E. E., *Can. J. Chem.* **1985**, *63*, 2362.
16. Quast, H.; Ivanova, S.; Peters, E.-M.; Peters, K., *Eur. J. Org. Chem.* **2000**, 507.
17. Kamigata, N.; Kawakita, O.; Izuoka, A.; Kobayashi, M., *J. Org. Chem.* **1985**, *50*, 398.
18. Xu, Y.; Zhu, S., *Tetrahedron* **1999**, *55*, 13725.
19. Alper, P. B.; Hung, S.-C.; Wong, C.-H., *Tetrahedron Lett.* **1996**, *37*, 6029.
20. Nyffeler, P. T.; Liang, C. -H.; Koeller, K. M.; Wong, C. -H., *J. Am. Chem. Soc.* **2002**, *124*, 10773.
21. Liu, Q.; Tor, Y., *Org. Lett.* **2003**, *5*, 2571.
22. Shainyan, B. A.; Meshcheryakov, V. I., *Russ. J. Org. Chem.* **2001**, *37*, 1797.

Trifluoromethanesulfonyl Chloride[1]



[421-83-0] $CClF_3O_2S$ (MW 168.53)
InChI = 1/CClF3O2S/c2-8(6,7)1(3,4)5
InChIKey = GRGCWBWNLSTIEN-UHFFFAOYAL

(trifluoromethylsulfonation agent;[1] chlorinating agent;[2] metal-catalyzed chlorotrifluoromethylation of alkenes[3])

Alternate Name: triflyl chloride.
Physical Data: bp 29–32 °C, *d* 1.583 g cm^{-3}.
Solubility: sol CH_2Cl_2, THF, dioxane.
Form Supplied in: colorless liquid, 99 +%.
Analysis of Reagent Purity: IR: 1424, 1306, 1237, 1115, 771, 611, 565, 532, 404 cm^{-1}.[4]
Preparative Methods: dried zinc trifluoromethanesulfonate is heated with $PCl_5 \cdot 2ZnCl$ at 260 °C. Fractional distillation of the volatile products gives TfCl (94% yield).[5]
Handling, Storage, and Precautions: moisture sensitive; store under N_2 in the cold. This toxic reagent is corrosive and is a lachrymator. It should only be handled in a fume hood.

Original Commentary

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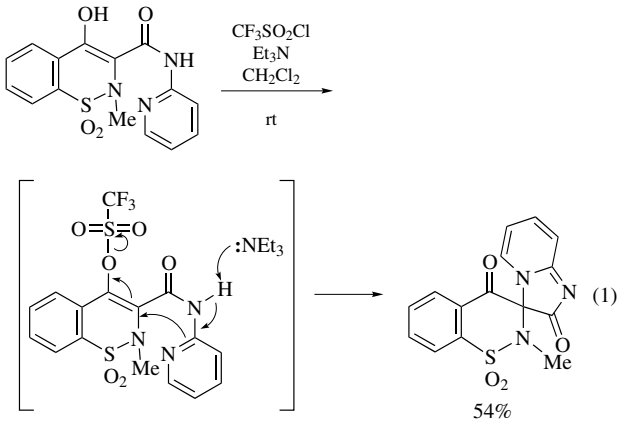
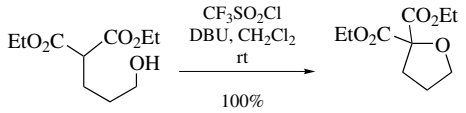
Triflate and Triflamide Formation. Triflyl chloride (TfCl) reacts as an electrophile with oxygen and nitrogen nucleophiles to produce triflate or triflamide derivatives. The trifluoromethanesulfonate group is a highly electron-withdrawing moiety and is a useful leaving group in organic synthesis for nucleophilic displacement, solvolysis, and metal-catalyzed coupling reactions.[1] The sulfonation reaction works well with amines[6] and alcohols, and is especially suitable for phenols.[7] An amine base such as triethylamine or diisopropylethylamine is usually added as an acid scavenger and to activate the substrates; however, the reactivity of the starting materials can be increased with prior anion formation by a stronger base.[8] Less reactive substrates may be sulfonated using trifluoromethanesulfonic anhydride or other derivatives of triflic acid such as those formulated from imidazole[9] or amides.[10] These are the reagents of choice for the formation of enol triflates from carbonyl compounds having α-hydrogens.[1] Mixed sulfonic anhydrides can be formed by reaction of the silver salt of an alkylsulfonic acid with triflyl chloride.[11]

An enol has been activated toward intramolecular nucleophilic addition with TfCl (eq 1).[12] A pyridine heterocycle reacts in a similar way.[13] In these reactions the triflinate anion ($CF_3SO_2^-$) functions as the leaving group. This sulfinate anion has also been studied as a nucleophile and potassium trifluoromethanesulfinate may be prepared by the reduction of TfCl with potassium iodide.[14]



(1)

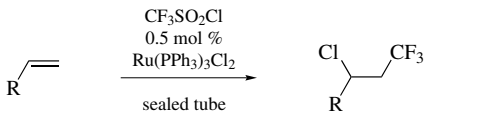
Chlorination of Activated Methylenes. Triflyl chloride acts as a mild chlorinating reagent with certain carbon acids and nucleophiles.[15] Carbon acids in the pK_a range between diethyl malonate and methyl dichloroacetate react with TfCl in the presence of an amine base such as Et_3N or 1,8-diazabicyclo[5.4.0]undec-7-ene to replace one or two acidic hydrogens with chlorine. The reaction is highly selective with the rate of chlorination being at least 10^5 greater than the rate of sulfonation. Yields are generally excellent and the reagent is often much more efficient than other chlorinating agents such as *N*-chlorosuccinimide. This transformation has been utilized for the synthesis of 2,2-disubstituted tetrahydrofurans, pyrans, and pyrrolidines (eq 2).[16]



(2)

When triflyl chloride and sodium azide are added to carbon acids, a similar reaction is observed and the corresponding azides are obtained in 50–60% yields.[17] The reactive species in this transformation is thought to be $F_3CSO_2N_2$. Similar reactivity has been seen with TfCl and silver(I) nitrate. The intermediate $F_3CSO_2NO_2$ reacts with activated methylenes and potassium *tert*-butoxide to give nitro derivatives in fair yields.[18]

Metal-catalyzed Chlorotrifluoromethylation of Alkenes. dichlorotris(triphenylphosphine)ruthenium(II) catalyzes the reaction between triflyl chloride and alkenes to give vicinally chloro/trifluoromethyl-substituted alkanes with the extrusion of sulfur dioxide.[19] The reaction works well for alkenes bearing either electron-withdrawing or electron-donating substituents (eq 3). Terminal alkenes give the best yields but the reaction works with internal double bonds as well. Temperatures $\geq 120\,^{\circ}C$ are required for complete extrusion of sulfur dioxide. Treatment of the products with aqueous potassium hydroxide causes the elimination of HCl to give vinyltrifluoromethane derivatives. The same ruthenium catalyst promotes the reaction between triflyl chloride and arenes to give trifluoromethylated aromatic compounds.[20] Trifluoromethyl iodide, an alternative reagent for the introduction of the trifluoromethane group, is less convenient to work with since it is a gas at rt.[3]



(3)

R = Ph, 87%
R = *m*-$NO_2C_6H_4$, 79%
R = $Me(CH_2)_7$, 72%

First Update

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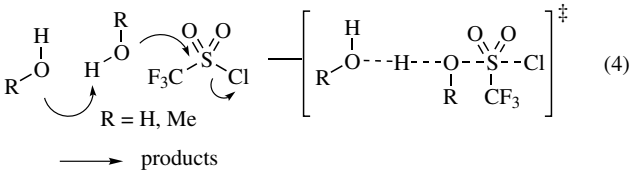
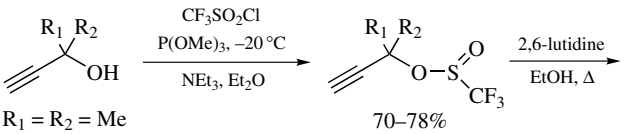
Solvolysis. The solvolytic reaction of trifluoromethanesulfonyl chloride in methanol and in water proceeds via a typical bimolecular reaction mechanism (S_AN/S_N2) in which the solvent molecules act as general base catalysts (eq 4).[21]



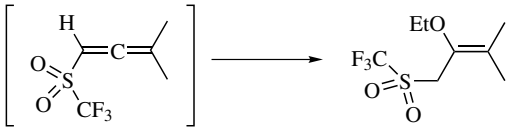
(4)

Reaction with Oxygen and Nitrogen Nucleophiles. Triflyl chloride reacts with many types of oxygen and nitrogen containing compounds, in the presence of a tertiary amine such as triethylamine, diisopropylethylamine, or substituted pyridines, to provide the corresponding triflates and triflamides. This reaction has been particularly developed on phenols, the corresponding aryl triflates being substrates of choice for metal-catalyzed cross-coupling reactions.[22] Aryl triflates can also be efficiently reduced to the corresponding arenes through a palladium-catalyzed process in the presence of bidendate phosphine ligands.[23,24] Propargylic alcohols have been efficiently transformed into trifluoromethyl sulfinates upon treatment with triflyl chloride and trimethyl phosphite (70–78% yield) (eq 5).[25] These esters can undergo a [2,3]-sigmatropic rearrangement to the corresponding allenyl trifluoromethyl sulfones. In the presence of an alcohol, a subsequent nucleophilic addition to the allenic β-carbon led to allyl triflones. 1,1-Disubstituted allylic alcohols were similarly transformed into allylic trifluoromethyl sulfinates.[26] These esters rearranged spontaneously to the corresponding γ,γ- and α,α-dimethylallyl triflones in 60% overall yield (eq 6).



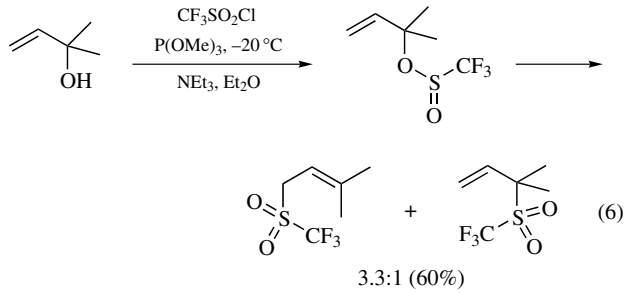
$R_1 = R_2 = Me$
$R_1 = Me$, $R_2 = Et$
$R_1 = Me$, $R_2 = H$

70–78%



(5)

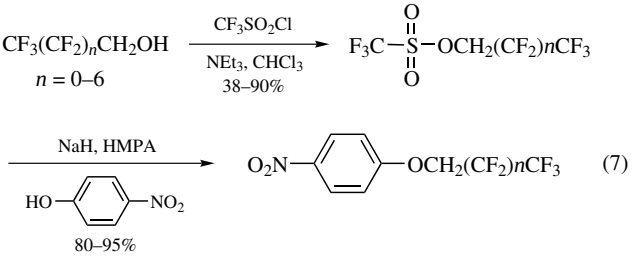
65%



(6)

3.3:1 (60%)

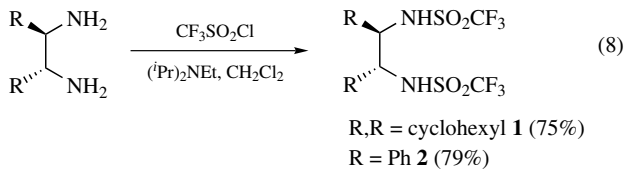
Triflyl chloride was also used for the preparation of fluoroalkyl trifluoromethanesulfonates that act as highly efficient fluoroalkylating reagents, 10^4 times more reactive than the corresponding tosylates.[27] Significant formation of fluoroalkyl ether side-products was observed when trifluoromethanesulfonyl fluoride was used.[28] Fluoroalkyl *p*-nitrophenyl ethers were thus prepared in high yields, without side-elimination reactions (eq 7).[29]



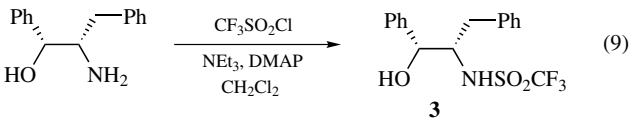
(7)

In some cases, triflyl chloride is also capable of acting as a chlorinating agent, leading to alkyl chlorides instead of alkyl triflates.[30]

Recent developments of triflyl chloride mediated *N*-sulfonation concentrated on the efficient preparation of chiral ligands for asymmetric transformations. Since the first report of Ohno[31] on the highly enantioselective addition of diethylzinc to aldehydes promoted by $Ti(O^iPr)_4$ complexed to simple chiral bis-triflamide **1** (eq 8), many studies have been devoted to the discovery of new sulfonamido-based ligands for this kind of transformations. (1*R*,2*S*)-1,3-Diphenyl-2-aminopropanol was reacted with triflyl chloride to provide the corresponding triflamide **3** in 70% yield (eq 9).[32] This ligand provided 73% ee in the asymmetric addition of diethylzinc to benzaldehyde. A binaphthyl-based trifluorosulfonamido alcohol was prepared in the presence of trifluoromethanesulfonic anhydride and resulted in 99% ee in the same transformation.[33] The bis-triflamide **2** was also used for the activation of carbonyl compounds in Mukaiyama-aldol reactions with silyl ketene acetals, providing optically active aldols in a moderate 22–31% ee.[34] This chiral Brønsted-acid catalyst was also used for catalytic enantioselective Friedel–Crafts reactions. Triflyl chloride was also reported for the synthesis of bis(*N*-sulfonylamino) phosphine-oxazoline ligands[35] that have been developed for asymmetric palladium-catalyzed allylic substitutions.



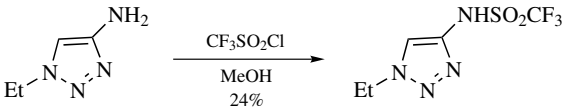
(8)



(9)

Trifluoromethanesulfonamides have been introduced in many biologically relevant compounds and represent important chemical motifs for the development of new pharmacophores. An illustrative example is given by the synthesis of a family of trifluoromethanesulfonamide analogues of Nimesulide that present inhibitory activity against cyclooxygenase-2 and in vivo anti-inflammatory properties.[36] Substitution of benzodiazepine derivatives by a trifluoromethanesulfonyl group enhanced their inhibitory activity toward mitochondrial ATP hydrolase.[37]

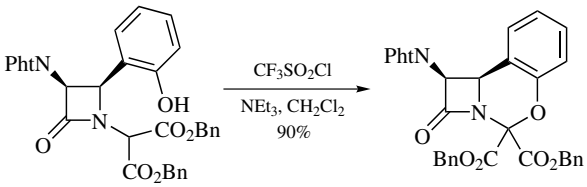
Other nitrogen nucleophiles can react efficiently with triflyl chloride. Below −30 °C, 1,1-dimethylhydrazine was sulfonated to afford the corresponding trifluoromethanesulfonic hydrazide.[38] In the azole series, the side chain of some 1,2,3-triazoles was functionalized with a trifluoromethanesulfonyl group (eq 10).[39] When pentafluoroethanesulfonyl chloride was used in this transformation, a mixture of mono- and di-sulfonylated derivatives was obtained. The reaction of triflyl chloride with a triazole carboxamide was proposed for the formation of a highly nucleofugal CF_3SO_2NH group which underwent methanolysis to the corresponding triazole carboxylate.[40]



(10)

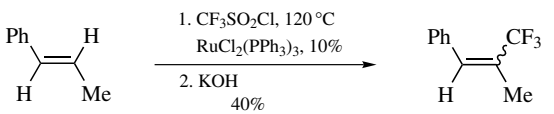
Some polysulfanes have also been reacted with triflyl chloride. In particular, iron sulfanes of the type $(\mu\text{-}S_x)[CpFe(CO)_2]_2$ were converted into thiosulfonato complexes[41] to study the mechanism of sulfur–sulfur bond formation during the Claus process.

Chlorination of Activated Methylene Groups. Triflyl chloride was used for the high yielding chlorination of carbon acids, and this reaction was applied to the synthesis of simple 2,2-disubstituted heterocycles.[16] This method has been extended to the preparation of heterocycles fused with β-lactams. Treatment of a hydroxyphenylazetidinone with triflyl chloride and triethylamine afforded a hemiaminal in 90% yield, through the chlorination of the dibenzyl malonate moiety (eq 11).[42] Performing the same transformation on a mercapto-β-lactam precursor led to the formation of a sulfenyl chloride intermediate rather than to chlorination of the malonate moiety.[43]

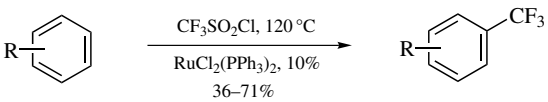


(11)

Perfluoromethylation of Alkenes, Aromatics and Heteroaromatics. Perfluoroalkylsulfonyl chlorides react with acyclic and cyclic alkenes in the presence of ruthenium(II) catalysts to produce chloroperfluoroalkanes with extrusion of sulfur dioxide.[44] Dehydrochlorination can be subsequently performed to produce perfluoroalkyl olefins (eq 12).[45] Radical reactions[46] and electrochemical methods[47] were less efficient and generated many side-products. Arenes were also reacted with triflyl chloride and other perfluoroalkylsulfonyl chlorides in the presence of $RuCl_2(PPh_3)_3$ catalyst at 120 °C for the replacement of a hydrogen atom of the aromatic nucleus by perfluoroalkyl groups.[48] Substituted benzenes led to a mixture of regioisomers (eq 13). The reaction proceeds through a perfluoroalkyl radical that adds to the aromatic ring to produce a cyclohexadienyl radical that undergoes hydrogen abstraction.

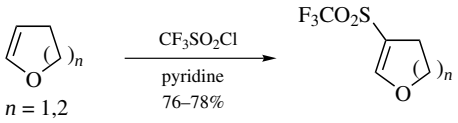


(12)



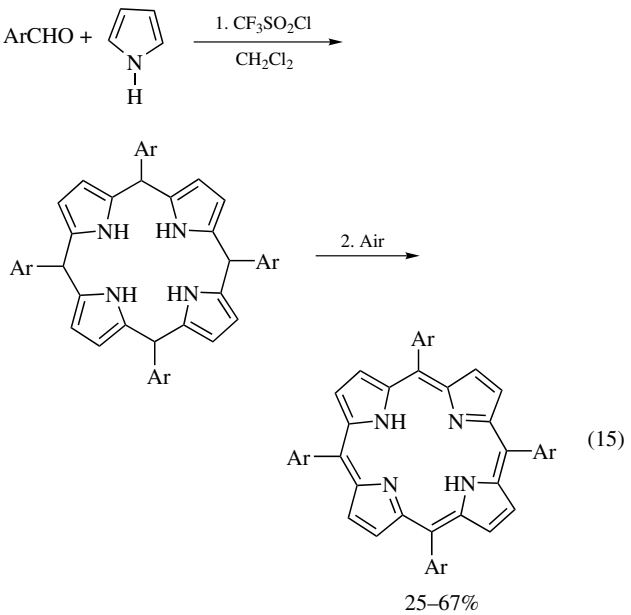
(13)

Furans, thiophenes and *N*-protected pyrroles reacted similarly with tridecafluorohexanesulfonyl chloride to afford the corresponding 2-tridecafluorohexyl heteroaromatics in moderate to good yields and high regioselectivity. The use of ruthenium (II)–chiral phosphine complexes produced low asymmetric inductions (9–15% ee) in the addition of methanesulfonyl chloride to styrene derivatives.[49] Triflyl chloride was also reacted with silyl enol ethers in the presence of ruthenium(II) phosphine complexes. Trifluoroalkylation was observed in the case of silyl enol ethers bearing electron-withdrawing groups whereas chlorination occurred for silyl enol ethers substituted by electron-donating groups.[50] Vinyl trifluoroalkylsulfones were produced with good yields through the reaction of triflyl chloride with vinyl ethers in the presence of pyridine (eq 14).[51] These vinyl triflones are substrates of choice to undergo nucleophilic attacks and dipolar cycloadditions.



(14)

Synthesis of Tetraarylporphyrins. Triflyl chloride was used under aerobic oxidation conditions to produce tetraarylporphyrins from pyrrole and various aromatic aldehydes.[52] The reaction proceeds through condensation of pyrrole to the aromatic aldehyde to form an intermediate aryl triflate which then undergoes polymerization and cyclization of the tetrapyrrolic oligomer. Air oxidation of the porphyrinogen intermediate completes the sequence (eq 15).



(15)

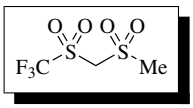
Other catalysts such as aluminum oxides, trifluoromethanesulfonic anhydride and thionyl chloride were less efficient. This mild method avoids the use of high temperature conditions and quinone oxidants.

Related Reagent. Trifluoromethanesufonic Anhydride.[53]

1. Stang, P. J.; Hanack, M.; Subramanian, L. R., *Synthesis* **1982**, 85.
2. Hakimelahi, G. H.; Just, G., *Tetrahedron Lett.* **1979**, 3645.
3. Kamigata, N.; Fukushima, T.; Terakawa, Y.; Yoshida, M.; Sawada, H., *J. Chem. Soc., Perkin Trans. 1* **1991**, 627.
4. (a) Pouchert, C. J. *Aldrich Library of FT-IR Spectra*; Aldrich: Milwaukee, 1989; Vol. 1, p 901B. (b) Robinson, E. A., *Can. J. Chem.* **1961**, *39*, 247.
5. (a) Tiers, G. V. D., *J. Org. Chem.* **1963**, *28*, 1244. (b) Haszeldine, R. N.; Kidd, J. M., *J. Chem. Soc* **1955**, 2901.
6. Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S., *Tetrahedron* **1992**, *48*, 5691.
7. (a) Keumi, T.; Saga, H.; Taniguchi, R.; Kitajima, H., *Chem. Lett.* **1977**, 1099. (b) Showalter, H. D. H.; Berman, E. M.; Johnson, J. L., *Tetrahedron Lett.* **1985**, *26*, 157. (c) Lau, C. K.; Bélanger, P. C.; Dufresne, C.; Scheigetz, J., *J. Org. Chem.* **1987**, *52*, 1670. (d) Reference 1.
8. Williams, H. W. R.; Rooney, C. S.; Bicking, J. B.; Robb, C. M.; de Solms, S. J.; Woltersdorf, O. W., Jr.; Cragoe, E. J., Jr., *J. Org. Chem.* **1979**, *44*, 4060.
9. Effenberger, F.; Mack, K. E., *Tetrahedron Lett.* **1970**, 3947.
10. Hendrickson, J. B.; Bergeron, R., *Tetrahedron Lett.* **1973**, 4607.
11. Moe, G. R.; Sayre, L. M.; Portoghese, P. S., *Tetrahedron Lett.* **1981**, 537.
12. Norris, C. P.; Berke, H.; Lombardino, J. G.; Bordner, J., *J. Heterocycl. Chem.* **1985**, *22*, 837.
13. Pasutto, F. M.; Knaus, E. E., *Can. J. Chem.* **1979**, *57*, 2371.
14. (a) Hendrickson, J. B.; Giga, A.; Wareing, J., *J. Am. Chem. Soc.* **1974**, *96*, 2275. (b) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S., *J. Org. Chem.* **1977**, *42*, 326.
15. (a) Hakimelahi, G. H.; Just, G., *Tetrahedron Lett.* **1979**, 3643. (b) Hafner, K.; Stowasser, B.; Sturm, V., *Tetrahedron Lett.* **1985**, *26*, 189. (c) Sato, K.; Kinoto, T.; Sugai, S., *Chem. Pharm. Bull.* **1986**, *34*, 1553.
16. Hakimelahi, G. H.; Just, G., *Tetrahedron Lett.* **1979**, 3645.
17. Hakimelahi, G. H.; Just, G., *Synth. Commun.* **1980**, *10*, 429.
18. Hakimelahi, G. H.; Sharghi, H.; Zarrinmayeh, H.; Khalafi-Nezhad, A., *Helv. Chim. Acta* **1984**, *67*, 906.
19. (a) Kamigata, N.; Sawada, H.; Suzuki, N.; Kobayashi, M., *Phosphorus Sulfur Silicon* **1984**, *19*, 199. (b) Kamigata, N.; Fukushima, T.; Yoshida, M., *J. Chem. Soc., Chem. Commun.* **1989**, 1559. (c) Ref. 3.
20. Kamigata, N.; Fukushima, T.; Yoshida, M., *Chem. Lett.* **1990**, 649.
21. Koo, S. I.; Yang, K.; Park, K. Y.; Woo, M. Y.; Cho, J. M.; Lee, J. P.; Lee, I., *Bull. Kor. Chem. Soc.* **2005**, *26*, 1241.
22. Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley and Sons: New York, 2002, Vol. 1.
23. Cabri, W.; De Bernardinis, S.; Francalanci, F.; Penco, S., *J. Chem. Soc., Perkin Trans. 1* (2) **1990**, 428.
24. Cabri, W.; Candiani, I.; Zarini, F.; Penco, S.; Bedeschi, A., *Tetrahedron Lett.* **1995**, *36*, 9197.
25. Braverman, S.; Pechenik, T.; Zafrani, Y., *Tetrahedron Lett.* **2001**, *42*, 1391.
26. Braverman, S.; Pechenik, T.; Zafrani, Y., *ARKIVOC* **2004**, *51*.
27. Hansen, R. L., *J. Org. Chem.* **1965**, *30*, 4322.
28. Burdon, J.; Mc Loughlin, V. C. R., *Tetrahedron* **1965**, *21*, 1.
29. Prescher, D.; Thiele, T.; Ruhmann, R., *J. Fluorine Chem.* **1996**, *79*, 145.
30. Shainyan, B. A.; Ustinov, M. V.; Nindakova, L. O., *Russ. J. Org. Chem.* **2001**, *37*, 1838.
31. Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S., *Tetrahedron* **1992**, *48*, 5691.
32. Wu, K. H.; Gau, H. M., *Organometallics* **2003**, *22*, 5193.
33. Kang, S. W.; Ko, D. H.; Kim, K. H.; Ha, D. C., *Org. Lett.* **2003**, *5*, 4517.
34. Zhuang, W.; Poulsen, T. B.; Jorgensen, K. A., *Org. Biomol. Chem.* **2005**, *3*, 3284.
35. Hilgraf, R.; Pfaltz, A., *Adv. Synth. Catal.* **2005**, *247*, 61.
36. Julémont, F.; de Leval, X.; Michaux, C.; Renard, J. F.; Winum, J. Y.; Montero, J. L.; Damas, J.; Dogné, J. M.; Pirotte, B., *J. Med. Chem.* **2004**, *47*, 6749.

37. Hamann, L. G.; Ding, C. Z.; Miller, A. V.; Madsen, C. S.; Wang, P.; Stein, P. D.; Pudzianowski, A. T.; Green, D. W.; Monshizadegan, H.; Atwal, K. S., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1031.
38. Shainyan, B. A.; Tolstikova, L. L.; Meshcheryakov, V. I.; Danilevich, Y. S., *Russ. J. Org. Chem.* **2004**, *40*, 1119.
39. Meshcheryakov, V. I.; Shainyan, B. A., *Russ. J. Org. Chem.* **2004**, *40*, 390.
40. Meshcheryakov, V. I.; Shainyan, B. A.; Tolstikova, L. L.; Albanov, A. I., *Russ. J. Org. Chem.* **2003**, *39*, 1517.
41. El-khateeb, M.; Shaver, A.; Lebuis, A. M., *J. Organomet. Chem.* **2001**, *622*, 293.
42. Hakimelahi, G. H.; Tsay, S. C.; Ramezani, Z.; Hwu, J. R., *Helv. Chim. Acta* **1996**, *79*, 813.
43. Hwu, J. R.; Hakimelahi, S.; Lu, K. L.; Tsay, S. C., *Tetrahedron* **1999**, *55*, 8039.
44. Kamigata, N.; Fukushima, T.; Terakawa, Y.; Yoshida, M.; Sawada, H., *J. Chem. Soc. Perkin Trans. 1* (3) **1991**, 627.
45. Roques, N.; Galvez, M.; Bonnefoy, A.; Larquetoux, L.; Spagnol, M., *Chim. Oggi* **2003**, *21*, 43.
46. Barton, D. H. R.; Lacher, B.; Zard, S. Z., *Tetrahedron* **1986**, *42*, 2325.
47. Muller, N., *J. Org. Chem.* **1986**, *51*, 263.
48. Kamigata, N.; Ohtsuka, T.; Fukushima, T.; Yoshida, M.; Shimizu, T., *J. Chem. Soc. Perkin Trans. 1* (10) **1994**, 1339.
49. Kamayama, M.; Kamigata, N.; Kobayashi, M., *J. Org. Chem.* **1987**, *52*, 3312.
50. Kamigata, N.; Udodaira, K.; Shimizu, T., *Phosphorus Sulfur Silicon Rel. Elem.* **1997**, *129*, 155.
51. Zhu, S.; Qin, C.; Xu, G.; Chu, Q., *Tetrahedron Lett.* **1998**, *39*, 5265.
52. Sharghi, H.; Hassani Nejad, A., *Tetrahedron* **2004**, *60*, 1863.
53. Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S., *Tetrahedron* **2000**, *56*, 3077.

Trifluoromethanesulfonylmethyl Methyl Sulfone



[93916-15-5] $C_3H_5F_3O_4S_2$ (MW 226.22)

InChI = 1/C3H5F3O4S2/c1-11(7,8)2-12(9,10)3(4,5)6/h2H2,1H3

InChIKey = YJEZMOWYAFJTBO-UHFFFAOYAL

(equivalent of alkene polyanion[1])

Alternate Name: mesyl triflone.

Physical Data: mp 115–116 °C.

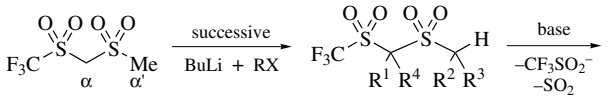
Solubility: insol cold H_2O; sol HCO_3^-, common organic solvents.

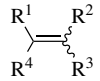
Preparative Methods: by triflation of dimethyl sulfone in base (EtMgBr/THF) with trifyl fluoride (CF_3SO_2F)[1] or by analogous sulfonylation of methyl triflone ($CH_3SO_2CF_3$)[2] with methanesulfonic anhydride.

Purification: recrystallized from H_2O, dried over P_2O_5 in vacuo.

Handling, Storage, and Precautions: stable solid, no known toxicity.

General Discussion. The reagent acts as an alkene polyanion equivalent ($^{2-}C{=}C^{2-}$) owing to successive alkylations of its di- or trianion followed by base-catalyzed cheletropic extrusion of SO_2 to form the product alkene (eq 1).[1]

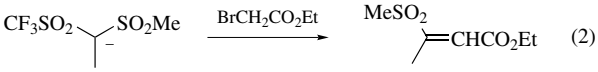




(1)

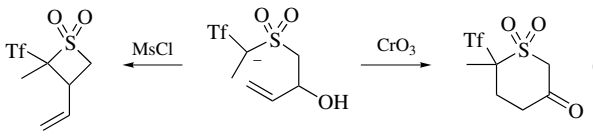
The successive alkylations, or reactions with other electrophiles, proceed with regiochemical control owing to the very different acidities of the two kinds of C–H bonds at α and α'. The most acidic proton (pK 4.3 in H_2O) is at α, and the dianion (2 mol butyllithium/THF at −78 °C) is also fully formed at the α-carbon. Alkylation of this dianion can yield either one or two alkylations at α, the former returning the stable anion of the α-monosubstituted reagent as product; the monoanion at α is very sluggish to alkylation. Successive alkylations, with added base (BuLi) and alkylating agent, proceed cleanly in the order R^1, R^2, R^3, R^4. With stoichiometric control of added base and carbon electrophile, as many as three substitutions may be carried out in one pot without isolation. Only when the α-carbon is fully substituted does treatment with base (t-BuO^- was the most effective[1]) afford the Ramberg–Bäcklund extrusion[3] of SO_2; otherwise, the presence of the stable α-anion precludes it. Although the regiochemistry of substitution is well controlled, the alkene stereochemistry of the product (eq 1) is not controllable.

The final substitution (R^4) requires very active alkylating agents and elevated temperatures unless it is a cyclization. α-Alkylations which provide carbonyl activation, as with α-halo carbonyls, give rise to elimination of triflinate directly (eq 2).[1]

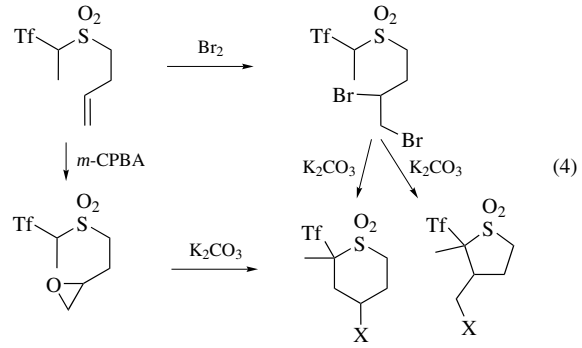


(2)

Acylation at α' is facile (on α,α'-dianions) and requires an extra equivalent of base for the acidic α-acyl sulfone products. Aldehydes and ketones react similarly at α' to afford β-hydroxy sulfones. Spontaneous cyclization occurred (eq 3) when the allylic alcohol from acrolein was oxidized to the unsaturated ketone (eq 3) and treatment with base completed the conversion to 3-methylcyclopentenone. However, mesylation of the β-hydroxy sulfone gave the four- instead of six-membered cyclization in eq 3 by direct rather than allylic displacement. Other cyclizations are shown in eq 4, the epoxide yielding only the six-membered ring, the dibromo derivative both five- and six-membered rings.

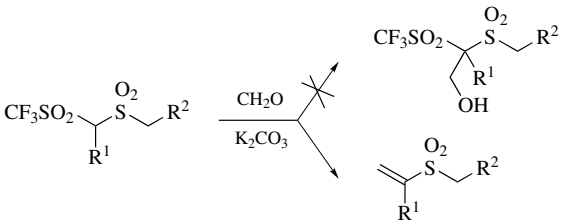


(3)



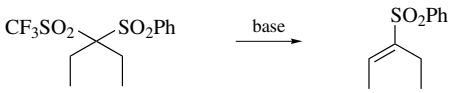
(4)

Reaction of the stable α-monoanion with formaldehyde quantitatively eliminates triflate ion to create α-methylene sulfones (eq 5).[4] Higher aldehydes did not react with the α-anion, but bromination is facile even at low temperature.



(5)

X-ray structures of several disulfones and their anions have been discussed,[5] and some related ones used in synthesis. The dimesyl analog ($MeSO_2CH_2SO_2Me$) also exhibits its dianion at α and is quite parallel in reactivity toward alkylation.[6] As expected, the α-monoanion is more reactive and more basic (pK = 12.5). When fully substituted at α the deprotonation of phenylsulfonyl methyl sulfones at α' also initiates the Ramberg–Bäcklund rearrangement with loss of phenylsulfinate ion.[7] When no α'-CH is available for deprotonation, treatment with base serves to eliminate triflinate, as in eq 6, and is also used to create cyclic vinyl sulfones when the α-dialkylation is done with α,ω-dihalides.[8]



(6)

In summary, the mesyl triflone reagent is useful for preparing 1,1-disubstituted alkenes (eq 1) (R^2 = R^3 = H) or cyclopentenones such as dihydrojasmone.[9] However, cyclohexenones were not formed[1] and, while more substituted acyclic alkenes are readily obtained, they arise as *cis–trans* mixtures.

1. Hendrickson, J. B.; Boudreaux, G. J.; Palumbo, P. S., *J. Am. Chem. Soc.* **1986**, *108*, 2358.
2. Koshar, R. J.; Mitsch, R. A., *J. Org. Chem.* **1973**, *38*, 3358.
3. Paquette, L. A., *Org. React.* **1977**, *25*, 1.
4. Hendrickson, J. B.; Palumbo, P. S., *Tetrahedron Lett.* **1985**, *26*, 2849.
5. Grossert, J. S.; Cameron, T. S.; Hoyle, J.; Roe, S. P.; Vincent, B. R., *Can. J. Chem.* **1987**, *65*, 1407.
6. Castro, A.; Spencer, T. A., *J. Org. Chem.* **1992**, *57*, 3496.
7. Ranasinghe, M. G.; Fuchs, P. L., *J. Am. Chem. Soc.* **1989**, *111*, 779. Scarpetti, D.; Fuchs, P. L., *J. Am. Chem. Soc.* **1990**, *112*, 8084.
8. Magar, S. S.; Fuchs, P. L., *Tetrahedron Lett.* **1992**, *33*, 745.
9. Hendrickson, J. B.; Palumbo, P. S., *J. Org. Chem.* **1985**, *50*, 2110.

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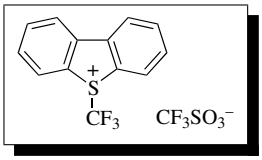
S-(Trifluoromethyl)dibenzothiophenium Triflate[1]



[129946-88-9] $C_{14}H_8F_6O_3S_2$ (MW 402.36)

InChI = 1/C13H8F3S.CHF3O3S/c14-13(15,16)17-11-7-3-1-5-9(11)10-6-2-4-8-12(10)17;2-1(3,4)8(5,6)7/h1-8H;(H,5,6,7)/q+1;/p-1/fC13H8F3S.CF3O3S/qm;-1

InChIKey = QXXHXTRTGZBOGD-NYGDWXCZCH

(trifluoromethylating agent for many nucleophilic substrates)

Physical Data: mp 155 °C.

Solubility: sol MeCN, DMF, DMSO; slightly sol THF, CH_2Cl_2; insol Et_2O.

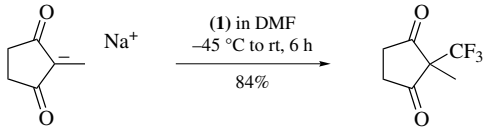
Form Supplied in: white crystals; commercially available.

Analysis of Reagent Purity: ^1H and ^{19}F NMR, IR.

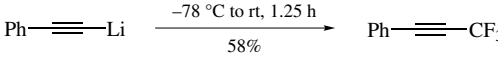
Purification: recrystallization from CH_3CN/Et_2O at rt.

Handling, Storage, and Precautions: nonhygroscopic and thermally stable crystals; should be stored in a dry atmosphere protected from light.

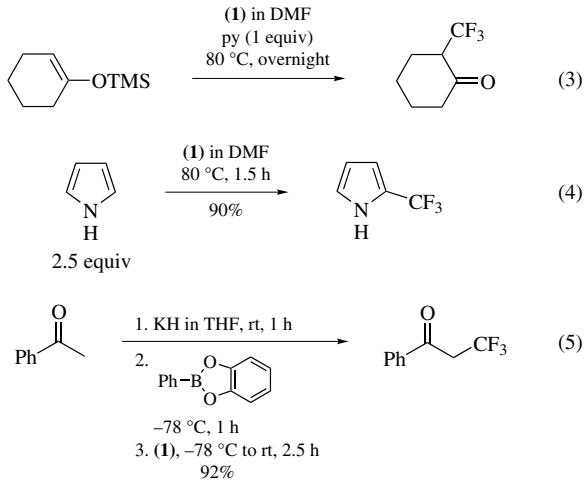
Trifluoromethylation.[1,2] *S*-(Trifluoromethyl)dibenzothiophenium triflate (**1**) is an electrophilic trifluoromethylating agent. Other related useful trifluoromethylating agents are *S*-(trifluoromethyl)-3,7-dinitrodibenzothiophenium triflate (**2**) and *Se*-(trifluoromethyl)dibenzoselenophenium triflate (**3**). The trifluoromethylating power order of these compounds varies as (**3**) < (**1**) < (**2**). The strongest reagent (**2**) smoothly fluorinates less reactive nucleophiles, while the mildest reagent (**3**) satisfactorily reacts with the more reactive nucleophiles. The title reagent (**1**) trifluoromethylates nucleophiles of intermediate reactivity. Thus (**1**) can trifluoromethylate metal salts of active methylene compounds (eq 1), acetylides (eq 2), enamines, enol silyl ethers (eq 3), reactive aromatics, heteroaromatics (eq 4), arenethiolates, and iodide anions in good yields. Enolate anions are trifluoromethylated in high yields by (**1**) in the presence of an equivalent amount of 2-phenylbenzo-1,3-dioxa-2-borole (eq 5).[3]



(1)



(2)



While (**1**) cannot trifluoromethylate triphenylphosphine, the more powerful reagent (**2**) provides access to (trifluoromethyl)triphenylphosphonium triflate in 78% yield. While (**1**) reacts with an alkanethiolate to give a trifluoromethyl alkyl sulfide in 47% yield along with 30% of a dialkyl disulfide as a byproduct, (**3**) produces a trifluoromethyl alkyl sulfide in 87% yield. The powerful trifluoromethylating agent (**2**) readily reacts with activated aromatics and heteroaromatics to yield trifluoromethylated compounds in good yields. Triflates (**1**)–(**3**) are all commercially available. The corresponding perfluoroalkyl analogs, *S*-(perfluoroethyl)-, -(perfluorobutyl)-, and -(perfluorooctyl)dibenzothiophenium triflates, are also available. Similar perfluoroalkylations are expected.[1] Since (**3**) is much more reactive than (**1**), the stability decreases, and (**3**) should be stored in a refrigerator.

1. Umemoto, T.; Ishihara, S., *J. Am. Chem. Soc.* **1993**, *115*, 2156.
2. Umemoto, T.; Ishihara, S., *Tetrahedron Lett.* **1990**, *31*, 3579.
3. Umemoto, T.; Adachi, K., *J. Org. Chem.* **1994**, *59*, 5692.

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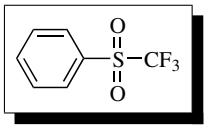
Trifluoromethyl Phenyl Sulfone



[426-58-4] $C_7H_5F_3O_2S$ (MW 210.18)
InChI = 1/C7H5F3O2S/c8-7(9,10)13(11,12)6-4-2-1-3-5-6/h1-5H
InChIKey = UPGBQYFXKAKWQC-UHFFFAOYAH

(reductive trifluoromethylating agent;[1] alkoxide- or hydroxide-induced nucleophilic trifluoromethylating agent;[2] benzenesulfonylation agent to prepare phenyl sulfones[3] and benzenesulfonic acid derivatives[2,4,5])

Physical Data: bp 205 °C; *d* 1.423 g cm^{-3} (20 °C).[6]

Solubility: soluble in alcohols, ethers, CH_2Cl_2, $CHCl_3$, DMF, and DMSO.

Form Supplied in: colorless liquid; often prepared by the oxidation of trifluoromethyl phenyl sulfide using aqueous hydrogen peroxide in acetic acid.[7]

Handling, Storage, and Precautions: $PhSO_2CF_3$ has high reactivity with bases and reducing metals; store under anhydrous, neutral conditions; use in a fume hood.

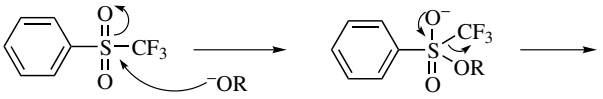
Reductive Trifluoromethylation. Since the trifluoromethanesulfonyl group (CF_3SO_2–) is a substituent with extreme electron-acceptor properties, trifluoromethyl phenyl sulfone can readily accept one electron to form a radical anion species.[8] Magnesium metal has been found to be a good single-electron transfer (SET) agent for trifluoromethyl phenyl sulfone and other similar systems.[1,9,10] The trifluoromethyl phenyl sulfone radical anion undergoes carbon-sulfur bond cleavage to give the trifluoromethyl anion (CF_3^-) species, which acts as a nucleophilic trifluoromethylating source for electrophiles. Hence, when trifluoromethyl phenyl sulfone reacts with magnesium metal and chlorotrimethylsilane in DMF at 0 °C, (trifluoromethyl)trimethylsilane (TMS-CF_3) is formed in high yield (eq 1).[1] Diphenyl disulfide is also formed as a by-product. It is well known that trifluoromethyl phenyl sulfone can be readily prepared from trifluoromethane (CF_3H) and diphenyl disulfide. So the reductive trifluoromethylation method provides a novel and useful catalytic pathway (in diphenyl disulfide) for the production of TMS-CF_3 from trifluoromethane and chlorotrimethylsilane.[1]

$$PhSO_2CF_3 + Mg + (CH_3)_3SiCl \xrightarrow[83\%]{\text{DMF, 0 °C to rt}} (CH_3)_3SiCF_3 + PhSSPh \quad (1)$$

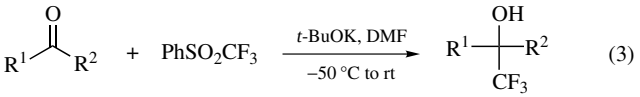
The magnesium-mediated reductive trifluoromethylation also works for other structurally diverse chlorosilanes. Chlorotriethylsilane, *t*-butyldimethylsilyl chloride, and tris(trimethylsilyl)silyl chloride have been applied to prepare corresponding trifluoromethyl-containing silanes.[1] However, the reductive trifluoromethylation did not take place with other electrophiles such as aldehydes, ketones, allyl bromide, benzyl chloride, or tributyltin chloride. Even tributyltin hydride and allyltrimethylsilane showed no reactivity.[1] The reason for such behavior is not clear. Probably, chlorosilanes play an important role during the reductive trifluoromethylation both as a silylating agent and a single-electron transfer promoter.

Alkoxide- or Hydroxide-induced Nucleophilic Trifluoromethylation. By using a nucleophilic base such as an alkoxide or hydroxide, the carbon-sulfur bond of trifluoromethyl phenyl sulfone can be cleaved to give a trifluoromethyl anion (CF_3^-) synthon that can undergo addition to carbonyl compounds (eq 2).[2] The driving force for this substitution is the formation of a strong S–O bond (348–551 kJ mol^{-1}) and the high polarity of the C–S bond of trifluomethyl phenyl sulfone. The generation of pseudohalide CF_3^- species is somewhat similar to the reaction between benzenesulfonyl halides with alkoxides.[2] Bases such as potassium *t*-butoxide, sodium methoxide, and potassium hydroxide can all be used as nucleophiles to activate the C–S bond

cleavage of trifluoromethyl phenyl sulfone and thus accomplish the trifluoromethylation to nonenolizable carbonyl compounds. Potassium *t*-butoxide was found to be the best choice in terms of reaction yields, and DMF or DMSO can be used as the reaction medium. Various nonenolizable aldehydes and ketones have been trifluoromethylated by this method to give corresponding trifluoromethyl-containing carbinols in good yields (eq 3).[2] An excess amount of potassium *t*-butoxide was found to be helpful to achieve high yields in the trifluoromethylation reactions for several reasons.[2] Due to the lower reactivity of ketones compared with aldehydes, the ketone reactions need a slightly longer time (2–3 h) for completion. With enolizable aldehydes and ketones, however, only low yields (10–30%) of trifluoromethylated products were observed because of the competing and facile aldol reactions. Another advantage of the reaction is the simple workup procedure. The by-product of the reaction is *t*-butyl benzenesulfonate, and it can be readily hydrolyzed into *t*-butyl alcohol and benzenesulfonic acid derivatives. Aqueous washing thus can remove most of the by-products and simplifies the purification process.



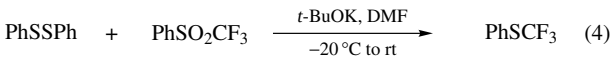
$$\boxed{''CF_3^-''} \qquad (2)$$



(3)

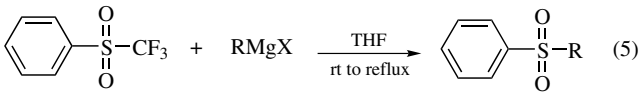
R^1= Ph, R^2= H, 77%;
R^1=Ph, R^2= Ph, 86%

The similar alkoxide- or hydroxide-induced trifluoromethylation was also found to work with other electrophiles.[2] Diphenyl disulfide can be trifluoromethylated to give trifluoromethyl phenyl sulfide in 87% yield (eq 4). Methyl benzoate can be trifluoromethylated to generate 2,2,2-trifluoroacetophenone in 30% yield at temperatures between −50 °C and −20 °C. Trifluoromethylcopper (CF_3Cu) can be generated in situ with trifluoromethyl sulfone, *t*-BuOK, and copper iodide (CuI), and it then further reacts with iodobenzene at 80 °C for 20 h to give α,α,α-trifluorotoluene in 26% yield.[2]



(4)

Benzenesulfonylation Reactions. Besides oxygen nucleophiles, carbon nucleophiles such as Grignard reagents and alkyllithiums also readily attack the sulfur center of trifluoromethyl phenyl sulfone to cleave the carbon-sulfur bond. Thus, trifluoromethyl phenyl sulfone can be used as a benzenesulfonylation agent with carbon nucleophiles to form phenyl sulfones (eq 5).[3] Primary saturated and allylic Grignard reagents are suitable for the reaction to give alkyl phenyl sulfones or allyl phenyl sulfones, with the yields ranging from 56 to 83%. Secondary Grignards can also react with trifluoromethyl phenyl sulfone satisfactorily, although elevated temperature is required in the case of isopropyl magnesium chloride.[3] *tert*-Butyl magnesium chloride did not react with trifluoromethyl phenyl sulfone even after reflux in THF overnight. When aryl Grignards are treated with trifluoromethyl phenyl sulfone, corresponding diaryl sulfones can be obtained in good yields. However, with vinyl magnesium bromide, consumption of trifluoromethyl phenyl sulfone without formation of the desired sulfone was observed at various temperatures.[3] *n*-Butyllithium also reacts with trifluoromethyl phenyl sulfone to give *n*-butyl phenyl sulfone in 38% yield.

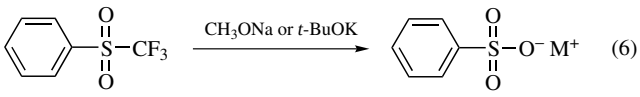


(5)

RMgX = CH_3MgBr, 77%;
= PhMgBr, 74%;
= allyl MgBr, 77%

The advantage of this methodology for sulfone preparation is that it can substantially avoid the formation of 1,1-disulfone, especially compared to the method using sulfonyl fluoride with organometallic reagents (such as Grignards and organolithium reagents). For the latter case, when an aliphatic organometallic species bearing an α proton is treated with a sulfonyl fluoride, 1,1-disulfones tend to arise through further deprotonation and sulfonylation of the initial product.[4,5] With the method using trifluoromethyl phenyl sulfone, no 1,1-disulfones were observed from the reactions with aliphatic Grignards or alkyllithium reagents.[3] The alkyl phenyl sulfone reaction products were undoubtedly metallated under the reaction conditions, but the resulting species were not sulfonylated by trifluoromethyl phenyl sulfone in contrast to their facile sulfonylation by sulfonyl fluoride.[3]

Another application of trifluoromethyl phenyl sulfone is in the preparation of benzenesulfonic acid (or metal benzenesulfonate) using oxygen nucleophiles. Trifluoromethyl phenyl sulfone is readily transformed into benzenesufonate salt upon treatment with an alkoxide or hydroxide (eq 6).[2,6,7] This is particularly useful for the convenient transformation of a polymer-supported trifluoromethyl phenyl sulfone into polymer-supported sulfonic acid (or sufonate) ion-conducting materials.[8–12]



(6)

M = Na, K

1. Prakash, G. K. S.; Hu, J.; Olah, G. A., *J. Org. Chem.* **2003**, *68*, 4457.
2. Prakash, G. K. S.; Hu, J.; Olah, G. A., *Org. Lett.* **2003**, *5*, 3253.
3. Steensma, R. W.; Galabi, S.; Tagat, J. R.; McCombie, S. W., *Tetrahedron Lett.* **2001**, *42*, 2281.
4. Shirota, Y.; Nagai, T.; Tokura, N., *Tetrahedron* **1969**, *25*, 3193.
5. Frye, L. L.; Sullivian, E. L.; Cusack, K. P.; Funaro, J. M., *J. Org. Chem.* **1992**, *57*, 697.
6. Barrera, M. D.; Cheburkov, Y.; Lamanna, W. M., *J. Fluorine Chem.* **2002**, *117*, 13.
7. Shein, S. M.; Krasnopol'skaya, M. I.; Boiko, V. N., *Zh. Obshch. Khim.* **1966**, *36*, 2141.
8. Yagupol'skii, L. M.; Marenets, M. S.; Kondratenko, N. V., *Zh. Obsh. Khim.* **1965**, *35*, 377.

9. Chen, Q.-Y.; Duan, J.-X., *J. Chem. Soc., Chem. Commun.* **1993**, 918.
10. Dunyashev, V. S., Polenov, E. A.; Grigor'ev, G. A.; Davtyan, A. G., *Zh. Fizich. Khim.* **1987**, *61*, 840. (English translation: *Russian J. Phys. Chem.* **1987**, *61*, 437.)
11. Prakash, G. K. S.; Hu, J.; Olah, G. A., *J. Fluorine Chem.* **2001**, *112*, 357.
12. Amii, H.; Kobaiyashi, T.; Hatamoto, Y.; Uneyama, K., *Chem. Commun.* **1999**, 1323.

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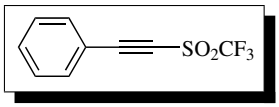
{[(Trifluoromethyl)sulfonyl]ethynyl}-benzene[1]



[52843-77-3] $C_9H_5F_3O_2S$ (MW 234.19)
InChI = 1/C9H5F3O2S/c10-9(11,12)15(13,14)7-6-8-4-2-1-3-5-8/h1-5H
InChIKey = LLBCLXNPGVYXFK-UHFFFAOYAX

(reactive dienophile, Michael acceptor, precursor to substituted vinyl sulfones, alkynylating agent)

Alternate Name: phenyl(trifluoromethanesulfonyl)acetylene; phenylethynyl trifluoromethyl sulfone.

Physical Data: mp 29.0–31.5 °C; bp 57–62 °C (0.1 mm Hg).

Preparative Methods: originally prepared by treatment of the lithium salt of phenylacetylene with trifluoromethanesulfonic (triflic) anhydride.[2] The corresponding sodium acetylide provides the title compound in higher yield.[3] Addition of the lithium salt to triflic anhydride (inverse addition) limits the production of unwanted by products.[4] Typical isolated yields are ~75%.

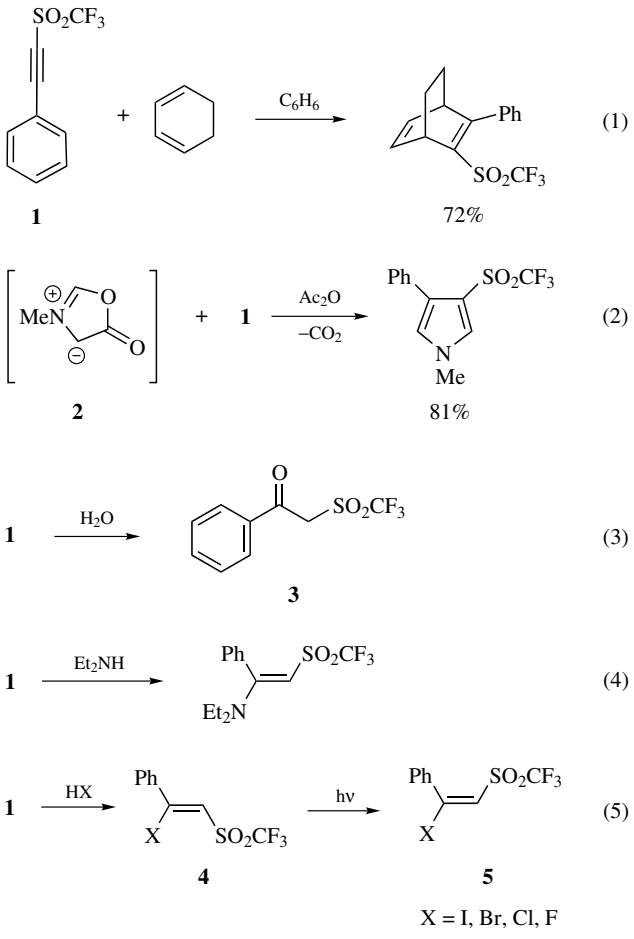
Purity: vacuum distillation; column chromatography (SiO_2).

Handling, Storage, and Precautions: moisture sensitive; thermally labile.

Cycloaddition Reactions. The trifluoromethylsulfonyl group is a powerful electron withdrawing substituent. Consequently, acetylenic trifluoromethyl sulfones (triflones) are activated toward reactions typical of electron deficient alkynes. Treatment of phenylethynyl trifluoromethyl sulfone (**1**) with conjugated dienes results in facile Diels–Alder cycloaddition.[2] Cyclopentadiene, 1,3-cyclohexadiene (eq 1), and 1,3-diphenylisobenzofuran, all give the reaction in good yield.

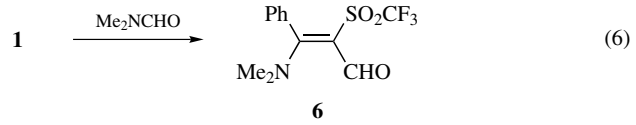
Kinetic experiments indicate that triflone **1** is a more reactive dienophile than dimethylacetylene dicarboxylate. The mesoionic intermediate **2** generated from *N*-formyl glycine and acetic anhydride reacts with **1** in a [3 + 2] fashion. The substituted pyrrole is obtained after loss of CO_2 (eq 2).[5]

Conjugate Addition Reactions. The electron withdrawing ability of the trifluoromethyl sulfonyl group renders triflone **1** particularly susceptible to the reaction with nucleophiles via conjugate addition. This property is also responsible for the moisture sensitivity of **1** as the reaction with H_2O affords the α-sulfonyl ketone **3** (eq 3).[3,6] Other nucleophiles, such as amines and alcohols, react with **1** to afford the corresponding enamines and enol ethers. The *E*-configured vinyl triflone isomers are the major or exclusive products (eq 4).[3,6] Reaction of **1** with other nucleophiles (benzoic acid, potassium phthalimide) gives *Z*-vinyl triflone products. Organocuprates and organocopper reagents also give the reaction.[7] Fuchs and co-workers have used acetylenic triflone **1** as a precursor of substituted vinyl halides.[4,6] Such vinyl halides proved to be suitable participants in palladium-catalyzed Stille-type cross-coupling reactions. Addition of HX (X = halide) across the alkynyl triple bond initially affords the *Z*-triflone **4** stereoselectively and in high yield. Isomerization of the alkene can then be effected under photochemical conditions to give *E*-triflone **5** (eq 5). Both **4** and **5** can be converted to more highly substituted vinyl triflones via application of standard cross-coupling reaction protocols.

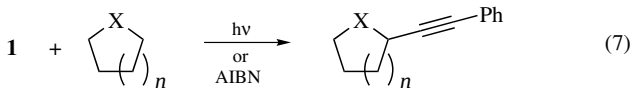


The initial product of conjugate addition to **1** is a sulfonyl-stabilized vinyl anion. This species can participate in subsequent reactions, particularly if an electrophilic center is present on the original nucleophilic moiety. An example of this reaction manifold is illustrated in eq 6.[8] Dimethylformamide is believed to serve first as a nucleophile in the conjugate addition to triflone **1**. The formamide then acts as an internal formylating agent leading to the production of **6**. The amphiphilic reactivity of **1** has

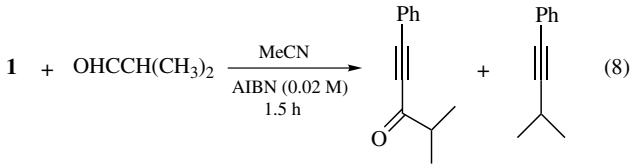
also been exploited in the preparation of various heterocyclic ring systems.[9,10]



Alkynylation of C–H Bonds. Perhaps the most intriguing reaction of acetylenic triflones (including **1**) involves the alkynylation of C-H bonds via a radical chain mechanism.[11] The reaction is initiated by light or traditional radical initiators (e.g., AIBN). The mechanism is believed to entail abstraction of a hydrogen atom from an unactivated C-H bond by the extremely electrophilic trifluoromethyl radical. The resulting alkyl radical then adds to triflone **1**, formally at the α-carbon, to generate a vinyl radical that collapses to an alkyne with concomitant loss of SO_2 and the chain propagating trifluoromethyl radical. Mechanistic studies have ruled out the intermediacy of vinylidene carbenes.[12] The reaction is of broad scope and a number of cyclic and acyclic hydrocarbons, ethers, and sulfides are regioselectively alkynylated in high yield (eq 7).[11] The reaction has proven suitable for the functionalization of crown ethers.[13] For transformations that require the use of a solvent, 1,2-dichloroethane and acetonitrile have given satisfactory results. It is noteworthy that heteroatom substituted vinyl triflones (readily prepared from **1** via conjugate addition—vide supra) are also effective alkenylating agents toward unactivated substrates (e.g., THF, cyclohexane).[6] Aldehydic C-H bonds are susceptible to alkynylation by **1** as well. Again, a radical chain mechanism has been proposed to account for this transformation. Mixtures of ethynyl ketone (major) and the corresponding decarbonylated (minor) products are usually obtained (eq 8).[14] The aldehydic C-H bond present in formate esters is unreactive under these conditions.



X = O, *n* = 1 (88%)
X = O, *n* = 2 (88%)
X = CH_2, *n* = 1 (63%)
X = CH_2, *n* = 2 (83%)



2.3:1.0
88%

1. Back, T. G., *Tetrahedron* **2001**, *57*, 5263.
2. Glass, R. S.; Smith, D. L., *J. Org. Chem.* **1974**, *39*, 3712.
3. Hanack, M.; Wilhelm, B.; Subramanian, L. R., *Synthesis* **1988**, 592.
4. Xiang, J. S.; Mahadevan, A.; Fuchs, P. L., *J. Am. Chem. Soc.* **1996**, *118*, 4284.
5. Berk, H. C.; Franz, J. E., *Synth. Commun.* **1981**, *11*, 267.
6. Xiang, J.; Jiang, W.; Gong, J.; Fuchs, P. L., *J. Am. Chem. Soc.* **1997**, *119*, 4123.
7. Xiang, J.; Fuchs, P. L., *J. Am. Chem. Soc.* **1996**, *118*, 11986.
8. Hanack, M.; Wilhelm, B., *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1057.
9. Kosack, S.; Himbert, G., *Chem. Ber.* **1987**, *120*, 71.
10. Barnes, K. D.; Ward, R., *J. Heterocycl. Chem.* **1995**, *32*, 871.
11. Gong, J.; Fuchs, P. L., *J. Am. Chem. Soc.* **1996**, *118*, 4486.
12. Xiang, J. S.; Fuchs, P. L., *Tetrahedron Lett.* **1996**, *37*, 5269.
13. Xiang, J.; Jiang, W.; Fuchs, P. L., *Tetrahedron Lett.* **1997**, *38*, 6635.
14. Gong, J.; Fuchs, P. L., *Tetrahedron Lett.* **1997**, *38*, 787.

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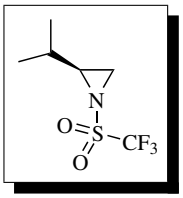
(*S*)-*N*-Trifluoromethylsulfonyl-2-isopropylaziridine



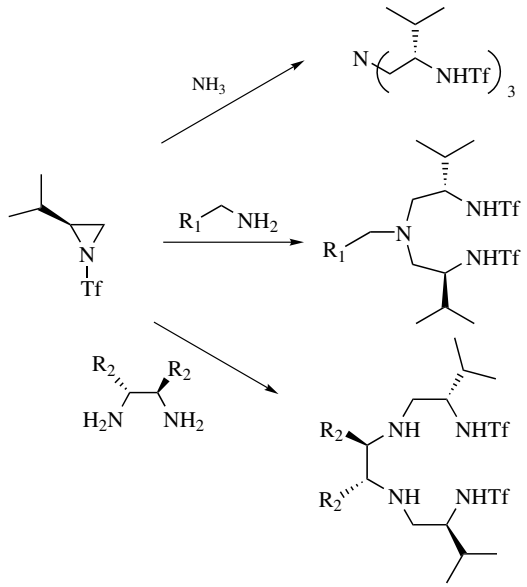
[196520-85-1] $C_6H_{10}F_3NO_2S$ (MW 217.21)
InChI = 1/C6H10F3NO2S/c1-4(2)5-3-10(5)13(11,12)6(7,8)9/h4-5H,3H2,1-2H3/t5-,10?/m1/s1
InChIKey = UKCBHEBTYNCWDW-UYBGKAFVBH

(reagent used as a chiral sulfonamide precursor in a wide array of reactions)

Physical Data: bp 186 °C; *d* 1.41 g cm^{-3}.
Solubility: soluble in most organic solvents.
Form Supplied in: colorless liquid; not commercially available. It is freshly prepared by treatment of (*S*)-valinol with triflic anhydride and triethylamine[1] at −78 °C.
Purification: it is quite unstable and is therefore used directly without further purification.
Handling, Storage, and Precautions: store under a nitrogen atmosphere and refrigerate. Decomposes on prolonged exposure to air.

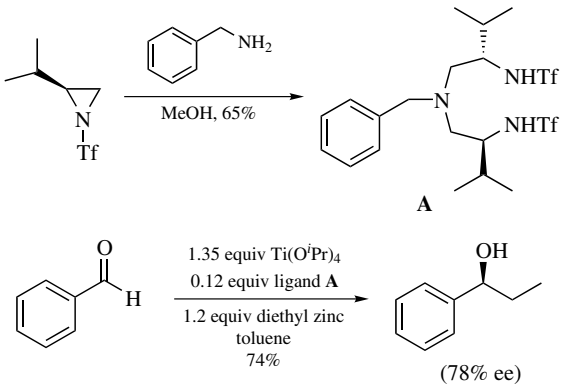
Precursor for Chiral Sulfonamide Ligands. Chiral sulfonamides are known to serve as versatile ligands for a variety of catalytic applications.[2] Nucleophilic ring opening of chiral activated aziridines with electron-withdrawing groups on the nitrogen atom permits extensive facile structural variations in the preparation of ligands carrying sulfonamide functionalities.[3] The nucleophilic attack generally occurs at the sterically least hindered carbon atom. Reaction of 3 equiv of aziridine with ammonia yields C_3-symmetric tris(sulfonamides).[4] But the reactions can be stopped after the introduction of merely 1 or 2 equiv of the aziridine, and thus afford mono as well as bis(sulfonamides). Reaction of primary amines with 2 equiv of aziridine yields bis(sulfonamide). Furthermore, tetradentate amines are accessible by

reaction of diamines with 2 equiv of aziridine (eq 1). The C_2- and C_3-symmetry ligands were assessed as catalysts in various asymmetric reactions.



(1)

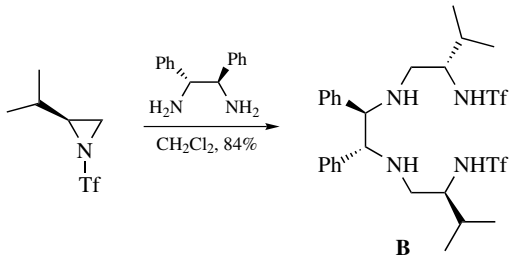
Titanium-mediated Additions of Diethylzinc to Aldehydes. The reaction of benzylamine with 2 equiv of (*S*)-*N*-trifluoromethylsulfonyl-2-isopropylaziridine afforded bis(sulfonamide) (**A**) in 65% yield (eq 2). This ligand was used as catalyst in the addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide to yield (*S*)-1-phenylpropanol in 78% ee.[4] Other ligands generated from ring opening of the aziridine with primary amines such as 2-(aminomethyl)pyridine and 2-aminophenol gave lower enantioselectivity. The addition of powdered 4 Å molecular sieves improved the yield as well as the enantioselectivity. Molecular sieves favor ligand exchange on Ti(IV) and thus formation of the active catalyst[5] (eq 3).



(2)

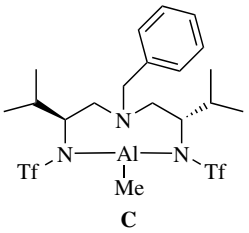
(3)

This methodology has also been employed for the preparation of tetradentate ligands by exchanging the primary amines for C_2-symmetric primary diamines (eq 4). For example, from (*R*,*R*)-1,2-diamino-1,2-diphenylethane, diastereomeric ligand **B** was obtained in 84% yield. These aromatic amines are sufficiently reactive to open the aziridine ring. Due to steric hindrance, no further reaction of the secondary amine moieties with (*S*)-*N*-trifluoromethylsulfonyl-2-isopropylaziridine was observed. This tetradentate ligand was inferior to bis(sulfonamides) as catalyst in the titanium-mediated addition of diethylzinc to benzaldehyde (59% ee compared with 78% ee).[3]

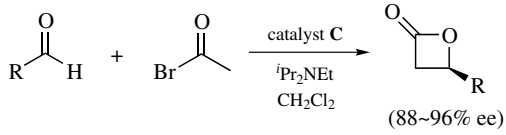


(4)

Acyl Halide–Aldehyde Cyclocondensation (AAC) Reactions. Treatment of C_2-symmetric ligand bis(sulfonamide) **A** with 1 equiv of trimethylaluminum generated the triamine–Al complex (**C**), which catalyzed the aldehyde ketene [2 + 2] cycladdition.



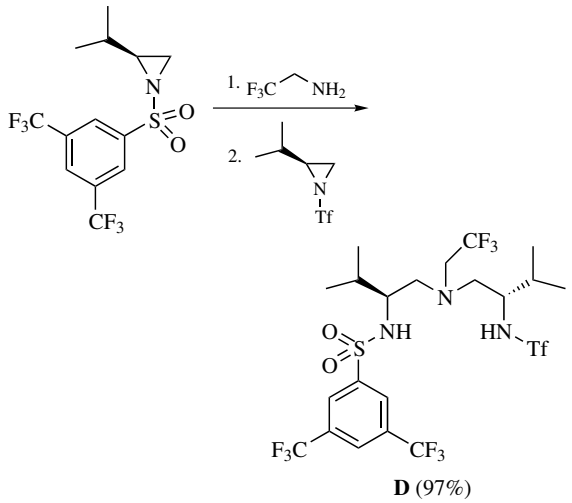
Under the influence of the triamine–Al catalyst, in situ generated ketene (formed from acyl bromide and diisopropylethylamine) reacted with aliphatic or aromatic aldehydes, affording β-lactone in excellent yield and 88∼96% ee[6] (eq 5). AAC reactions deliver enatioenriched β-lactone acetate aldol surrogates, which are direct progenitors of numerous chiral building blocks (β-amino acid,[7] allene,[8] and α,β-disubstituted carboxylic acids[9]).



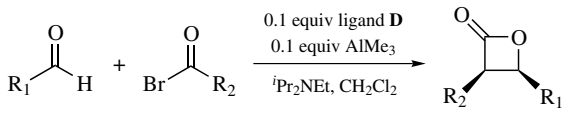
(5)

However, these first generation AAC reactions proved to be generally useful only for reactions involving unsubstituted ketene. To overcome the competing substituted ketene dimerization or trimerization under the AAC reaction conditions, second generation catalyst focused on retaining the essential four-coordinate, trigonal monopyramidal geometry while delivering enhanced metal electrophilicity. Unsymmetrical ligand **D** was designed and synthesized from (*S*)-*N*-trifluoromethylsulfonyl-2-isopropylaziridine.[10] Ring opening with 2,2,2-trifluoroethylamine and the corresponding second amine attacked the aziridine ring to give the unsymmetrical ligand **D** in 97% yield (eq 6).

The second-generation Al(triamine) catalyst (in situ generated from unsymmetrical ligand **D** with trimethylaluminum) induces substituted ketene AAC reactions exhibiting high levels of enantioselection (eq 7). Substitiuted ketene (R_2 = Me, ethyl, propyl) reacting with aliphatic or unsaturated aldeyde gave *cis*-β-lactone in 88∼96% ee.[10]

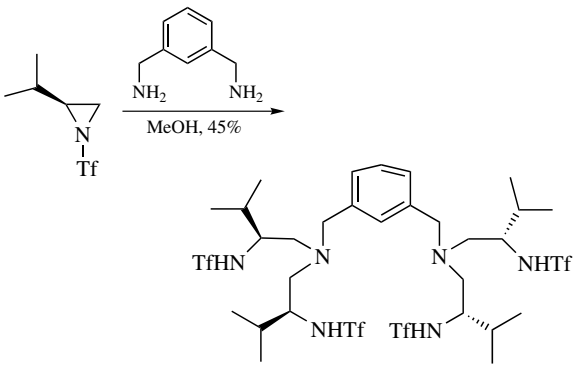


D (97%) (6)



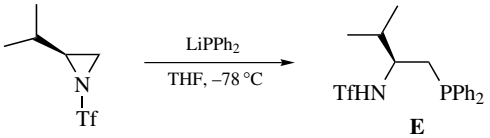
syn:*anti* 89:11~98:2
88~96% ee (7)

Asymmetric Hydrogenation. Reaction of *m*-xylenediamine with (*S*)-*N*-trifluoromethylsulfonyl-2-isopropylaziridine gave the tetradentate ligand in 45% yield. This tetradentate ligand–samarium complex gave excellent enantioselectivity in the asymmetric hydrogenation of acetophenone (up to 93% ee)[11] (eq 8).

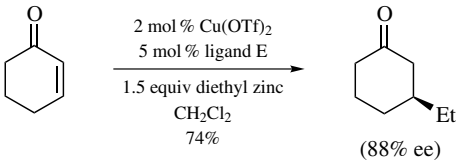


(8)

Cu-catalyzed Conjugate Addition of Dialkylzincs to Cyclic Enones. Nucleophilic ring opening of (*S*)-*N*-trifluoromethylsulfonyl-2-isopropylaziridine with diphenylphosphinelithium afforded phosphine sulfonamide ligand **E** [12] (eq 9). Employing $Cu(OTf)_2$ (2 mol %) as the catalyst precursor, phosphine sulfomamide lignd **E** (5 mol %) provided the conjugate addition product in 88% ee at ambient temperature (eq 10). An unusual relationship between temperature and enantioselectivity was observed in this reaction: A decrease in the temperature (−78 °C, 50% ee) or an increase in the temperature (38 °C, 85% ee) gave poor enantioselectivity. This phenomenon is highly dependent on the ligand:Cu ratio.



E (9)



(88% ee) (10)

Related Reagents. (*S*)-*N*-(Methylsulfonyl)-2-methylaziridine; (*S*)-*N*-(Methylsulfonyl)-2-isopropylaziridine; (*S*)-*N*-(Toluenesulfonyl)-2-methylaziridine; (*S*)-*N*-(Toluenesulfonyl)-2-isopropylaziridine.

1. (a) Cernerud, M.; Adolfsson, H.; Moberg, C., *Tetrahedron: Asymmetry* **1997**, *8*, 2655. (b) Nelson, S. G.; Mills, P. M.; Ohshima, T.; Shibasaki, M., *Org. Synth.* **2005**, *82*, 170.
2. Pu, L.; Yu, H.-B., *Chem. Rev.* **2001**, *101*, 757.
3. Lake, F.; Moberg, C., *Eur. J. Org. Chem.* **2002**, 3179.
4. Cernerud, M.; Skrinning, A.; Bérgère, I.; Moberg, C., *Tetrahedron: Asymmetry* **1997**, *8*, 3437.
5. Mikami, U.; Terada, M.; Nakei, T., *J. Am. Chem. Soc.* **1989**, *111*, 1940.
6. Nelson, S. G.; Peelen, T. J.; Wan, Z., *J. Am. Chem. Soc.* **1999**, *121*, 9742.
7. Nelson, S. G.; Spencer, K. L., *Angew. Chem., Int. Ed.* **2000**, *39*, 1323.
8. Wan, Z.; Nelson, S. G., *J. Am. Chem. Soc.* **2000**, *122*, 10470.
9. Nelson, S. G.; Wan, Z.; Stan, M. A., *J. Org. Chem.* **2002**, *67*, 4680.
10. Nelson, S. G.; Zhu, C.; Shen, X., *J. Am. Chem. Soc.* 2004, *126*, 14.
11. Mashima, K.; Ohno, K.; Matsumura, K., PCT Int. Appl. (2004), (WO 2004/069786 A1).
12. Krauss, I. J.; Leighton, J. L., *Org. Lett.* **2003**, *5*, 3201.

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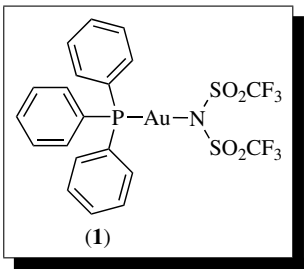
[1,1,1-Trifluoro-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamidato-κN](triphenylphosphine)



(**1**)

[866395-16-6] $C_{20}H_{15}AuF_6NO_4PS_2$ (MW 739.40)

InChI = 1/C18H15P.C2F6NO4S2.Au/c1-4-10-16(11-5-1)19(17-12-6-2-7-13-17)18-14-8-3-9-15-18;3-1(4,5)14(10,11)9-15(12,13)2(6,7)8;/h1-15H;;/q;-1;+1/rC18H15P.C2AuF6NO4S2/c1-4-10-16(11-5-1)19(17-12-6-2-7-13-17)18-14-8-3-9-15-18;3-10(15(11,12)1(4,5)6)16(13,14)2(7,8)9/h1-15H;

InChIKey = GJWZOHAPYGHXHP-KVELLCCTAD

(reagent mostly used as carbophilic Lewis acid for activation of alkynes/allenes toward nucleophilic attack and as an isolable alternative to unstable $Ph_3PAu^+ X^-$ (X = SbF_6, ClO_4, BF_4, OTf); used as a mild oxophilic Lewis acid)

Physical Data: mp > 100 °C (dec).

Solubility: soluble in most organic solvents including MeOH, CH_3CN, CH_2Cl_2, THF, EtOAc, diethyl ether, and toluene.[1]

Form Supplied in: white solid, not commercially available.

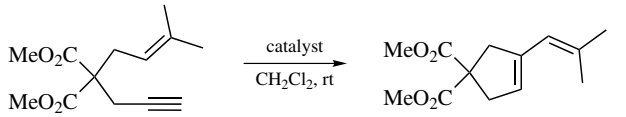
Preparative Methods: obtained quantitatively through metathesizing equivalent Ph_3PAuCl and $AgNTf_2$ in CH_2Cl_2, filtering AgCl off, and removing solvent.[1]

Handling, Storage, and Precautions: it is air stable[1] and not hygroscopic, but turns gray over time at room temperature due to slow decomposition. It should be stored in a freezer and can last for months.

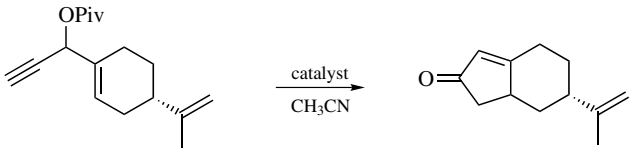
General Comments. Cationic Au(I) complexes, $[(Ph_3P)Au]^+ X^-$, are arguably the most used catalysts in Au research.[2,3] They are conveniently prepared from commercially available $(Ph_3P)AuCl$ via metathesis with AgX. X^- is mostly noncoordinating or weakly coordinating anion such as SbF_6^-, ClO_4^-, BF_4^-, OTf^-, and PF_6^-. However, these complexes are prone to decom-position and often generated and used in situ. Gagosz et al. reported that $(Ph_3P)AuNTf_2$ is stable and can be isolated as a white solid.[1] NTf_2^- is weakly coordinating, and the catalytic reactivity of $(Ph_3P)AuNTf_2$ is comparable to other cationic Au(I) complexes; moreover, there are practical advantages: there is no need to generate the cationic Au(I) complex each time, and the interference of Ag salts is excluded. In addition, due to its increased stability $(Ph_3P)AuNTf_2$ is therefore more suitable for slow reactions and reactions requiring higher temperatures.

The reactions described below are categorized according to the nature of the nucleophile that attacks the gold-activated alkynes/allenes. While complex **1** is emphasized, other cationic Au(I) complexes could in general catalyze these reactions as well.

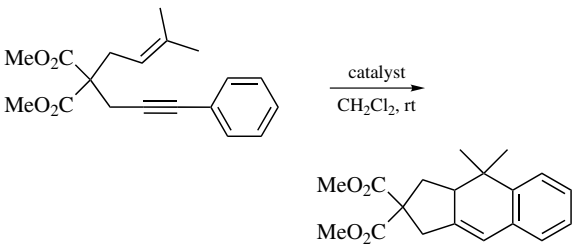
Carbon-based Nucleophiles: Cycloisomerization of Enynes and Allenynes. Gagosz et al. reported in their original study that complex **1** catalyzed enyne metathesis of **2** with high TON (9700) and in 97% yield (eq 1). In comparison, 2 mol % of $(Ph_3P)AuSbF_6$ (TON = 50) was needed for the same reaction.[4] In a Au-catalyzed Rautenstrauch reaction,[5,6] the reaction using **1** was much faster than the original $(Ph_3P)AuOTf$ and the reaction yield was improved (eq 2). Another advantageous example for using **1** instead of in situ generated $(Ph_3P)AuSbF_6$ is the intramolecular [4 + 2] cycloaddition of arylalkynes,[7] where a much faster reaction (1 h vs. 12 h) and a higher yield were realized (eq 3). Various other previously reported cationic Au(I) catalysis including Conia-ene,[8,9] propargyl Claisen rearrangement,[10] 1,5-enyne cycloisomerizations,[11] intramolecular alkyne hydroarylation,[12] and methoxycyclization of 1,6-enynes[13] were efficiently catalyzed by **1** as well.[1] A drastic reactivity difference between $AuCl_3$ and **1** was observed in allenyne cyclizations, attributed to a remarkable effect of Cl^- (eq 4).[14]



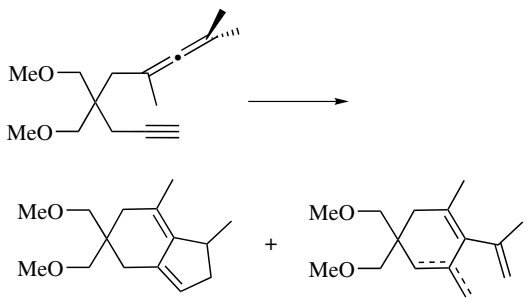
1 (0.01 mol %), 30 min	97%	
$(Ph_3P)AuSbF_6$ (2 mol %), 25 min	91%	(1)



1 (1 mol %), 5 °C, 75 min	81%	
$(Ph_3P)AuOTf$ (2 mol %), rt, 10 h	63%	(2)



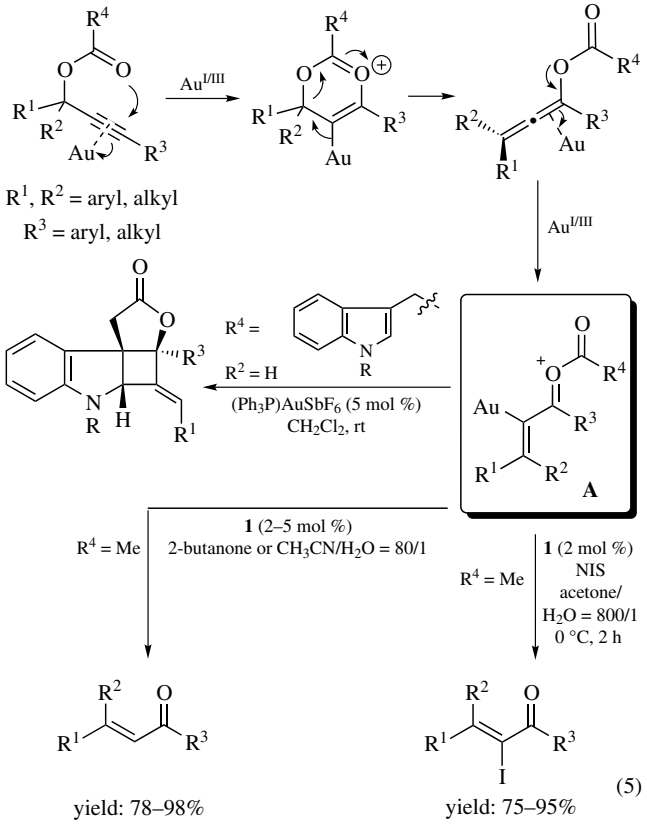
1 (2 mol %), 1 h	98%	
$(Ph_3P)AuSbF_6$ (2 mol %), 12 h	83%	(3)



$AuCl_3$, 1 mol % CH_2Cl_2, 0 °C, 0.5 h	80%	trace	
1, 1 mol % CH_2Cl_2, 0 °C, 6 h	5%	68%	(4)

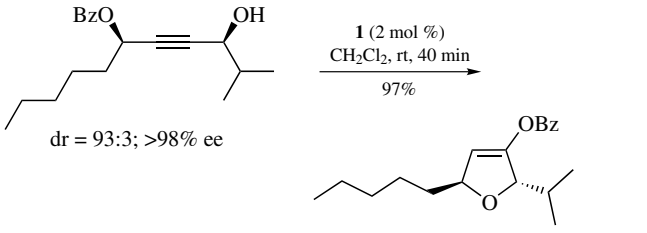
Oxygen-based Nucleophiles.

Propargylic Carboxylates as Substrate. In 2005, Zhang[15] demonstrated for the first time that the cationic gold(I) complex $(Ph_3P)AuSbF_6$, generated in situ, can catalyze tandem 3,3-rearrangement of propargylic carboxylates and subsequent activation of the in situ formed carboxyallene, leading to the formation of a highly functionalized Au-containing alkenyl oxocarbenium intermediate **A** (eq 5). Intermediate **A** underwent intramolecular [2 + 2] cycloaddition with a tethered indole ring, yielding tetracyclic highly functionalized cyclobutanes. This tandem process can be effectively catalyzed by complex **1** as well. An efficient preparative method for α,β-unsaturated enones[16] was developed by the same research group via hydrolyzing intermediate **A** In this study, simple acetates were used, and complex **1** was chosen for the ease of handling. The substrate scope is very general: substituents R^1, R^2, and R^3 can be either aryl groups of different electronic character (e.g., Ph, *p*-BrPh, *p*-MeO_2CPh) or various alkyl groups (e.g., ^{i}Pr, ^{t}Bu, cyclohexyl). This method is highly *E*-selective for substrates derived from aldehydes and can serve as a viable alternative to phosphorus-based methods. Furthermore, the Au–C(sp^2) bond in **A** could be iodinated, yielding synthetically useful α-iodoenones with excellent diastereoselectivity for β-monosubstituted products.[17] Again, the substrate scope is general, and this method is particularly useful for preparing linear products.

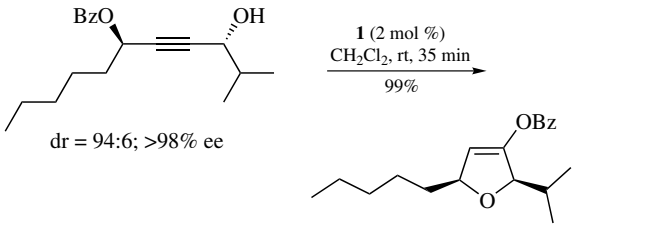


(5)

In 2006, Gagosz and coworkers developed a stereoselective synthesis of functionalized dihydrofurans from butynediol monobenzoates (eqs 6 and 7) using **1** as catalyst.[18] This reaction also employed an initial Au-catalyzed 3,3-rearrangement of propargylic carboxylates, followed by intramolecular stereoselective hydroalkoxylation of the distal C–C double bond of the in situ formed benzoyloxyallenes. High degree of stereoinversion at the carboxy end of the butyne was realized with less sterically hindered substrates.

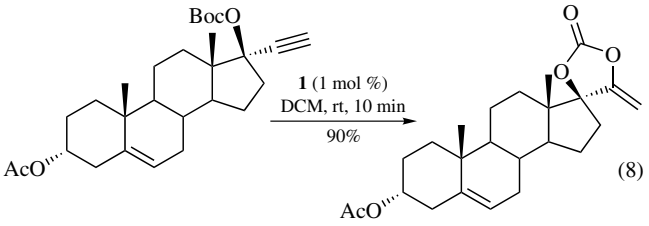


(6)

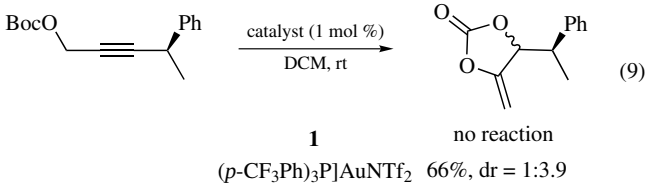


(7)

Propargylic/Homopropargylic tert-Butyl Carbonate as Substrate. 4-Alkylidene-1,3-dioxolan-2-ones were formed in mostly over 75% yields from propargylic *t*-butyl carbonates with terminal alkynes (eq 8). This reaction underwent initial **1**-catalyzed carbonyl 5-*exo*-*dig* cyclization followed by fragmentation of the *t*-butyl group into isobutene and a proton.[19] For substrates with internal alkynes, complex **1** was mostly inert, and more electron-deficient cationic Au(I) led to isomeric products (eq 9). A related study using homopropargylic *t*-butyl carbonates led to the formation of 4-methylene-1,3-dioxan-2-ones.[20] In this study, the more electron-deficient cationic Au(I) catalyst, $[(p\text{-}CF_3Ph)_3P]AuNTf_2$, was more effective.



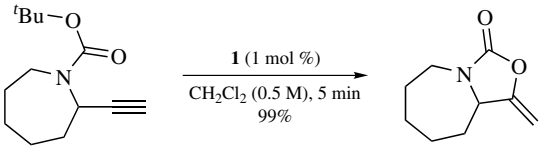
(8)



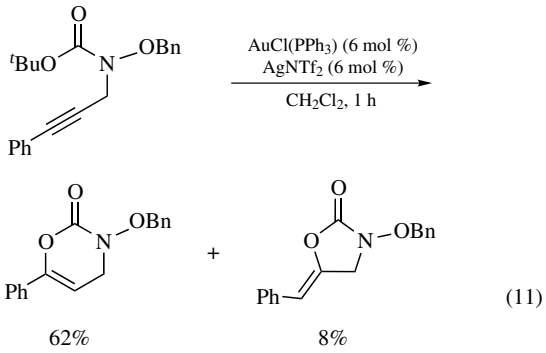
(9)

N-Propargylic/N-Alkynyl O-tert-Butyl Carbamate as Substrate. Similarly, *O-tert*-butylcarbamates derived from propargylic amines can undergo **1**-catalyzed carbonyl *5-exo-dig* cyclization, leading to 5-methylene-1,3-oxazolidin-2-ones in good yields (eq 10).[21] The reaction worked well with various substrates without substitution at the propargyl alkyne terminus; moreover,

the carbamate nitrogen could be either unsubstituted or substituted with an alkyl or aryl group. Interestingly, Takemoto et al. showed that the exclusive *5-exo-dig* cyclization mode observed by Gagosz could be switched to *6-endo-dig* selectivity using in situ generated **1** when the alkyne terminus was substituted and *N*-alkoxy carbamate substrates was used (eq 11).[22]

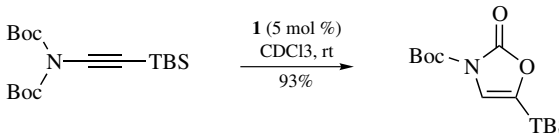


(10)



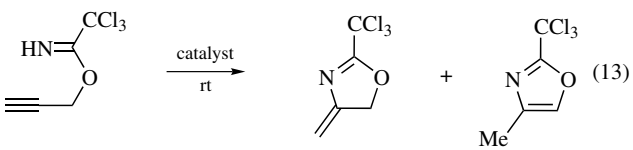
(11)

Hashmi et al. reported that *N*-alkynyl carbamates underwent **1**-catalyzed *5-endo-dig* cyclization, yielding oxazolinones. In this case, the nitrogen was substituted with another EWG in addition to the Boc moiety due to the need in substrate preparation and perhaps attenuating the reactivity of the ynamide moiety (eq 12).[23]



(12)

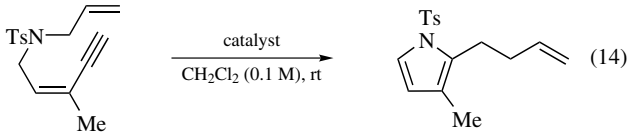
Nitrogen-based Nucleophiles. *5-exo-dig* cyclization of stable propargyl trichloroacetimidates surprisingly yielded methylideneoxazolines in a quantitative yield without aromatization (eq 13). In contrast, $AuCl_3$ as catalyst led to concurrent aromatization, indicating the mild nature of complex **1**.[24]



(13)

1 (1 mol %), CH_2Cl_2, 2 h	quant	–
$AuCl_3$ (3 mol %), $CHCl_3$, 12 h	1:1	

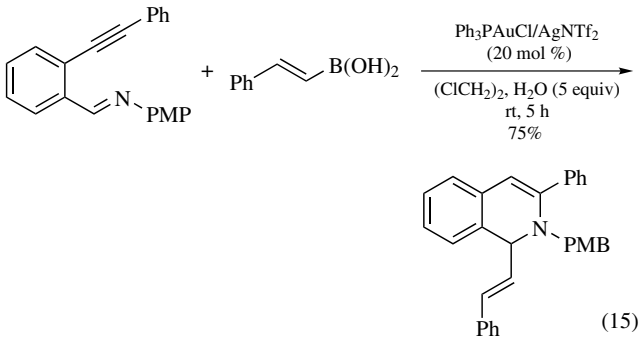
In a Au-catalyzed aza-Claisen-type rearrangement, complex **1** was effective, but less efficient than $(p\text{-}CF_3Ph)_3PAuNTf_2$ (eq 14).[25]



(14)

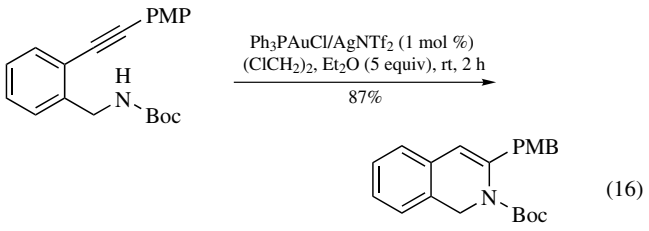
1 (2 mol %), 2 h	80%
$(p\text{-}CF_3Ph)_3PAuNTf_2$ (2 mol %), 0.5 h	94%

With *ortho*-substituted imine moieties, activation of arylalkynes by complex **1** as well as $In(OTf)_3$ and $NiCl_2$ led to *6-endo-dig* cyclization, forming isoquinolinium intermediates. These reactive intermediates were trapped with various nucleophiles including allylstannane, hydride from the Hantzsch salt, active methylene compounds, and alkenylboronic acids, yielding 1,2-dihydroisoquinolines (eq 15).[26]



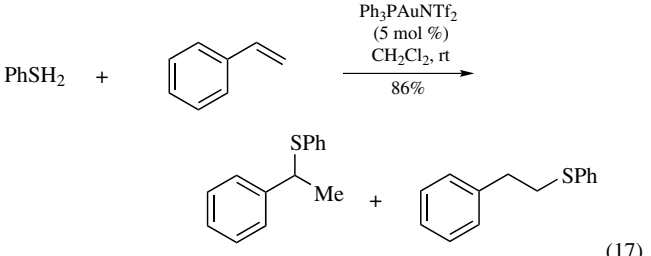
(15)

Similarly, arylalkynes with *ortho*-substituted carbamates cyclized via either *6-endo-dig* or *6-exo-dig* mode to form hydroisoquinolines.[27] Interestingly, the addition of EtOH (5 equiv) substantially accelerated the reactions (eq 16). This general strategy was used in the construction of the CDE ring system of tetrahydroisoquinoline alkaloids.[28]



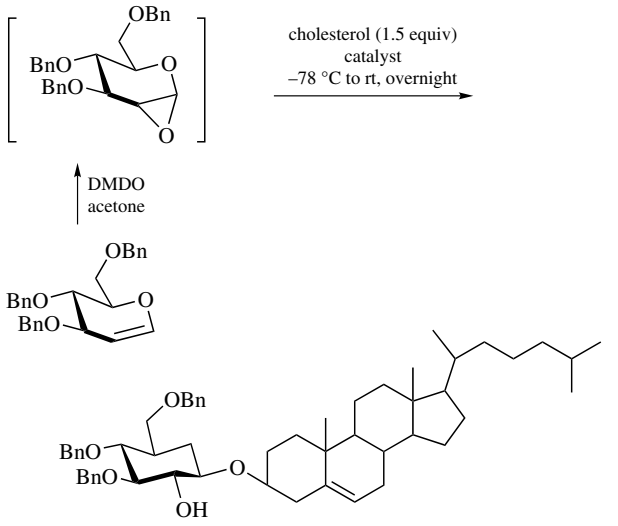
(16)

Hydrothiolation of Conjugated C–C Double Bonds. This reaction reported by He[29] was best catalyzed by Ph_3PAuBF_4 in most cases and showed excellent regioselectivity. Complex **1** was shown in one case as an effective catalyst (eq 17).



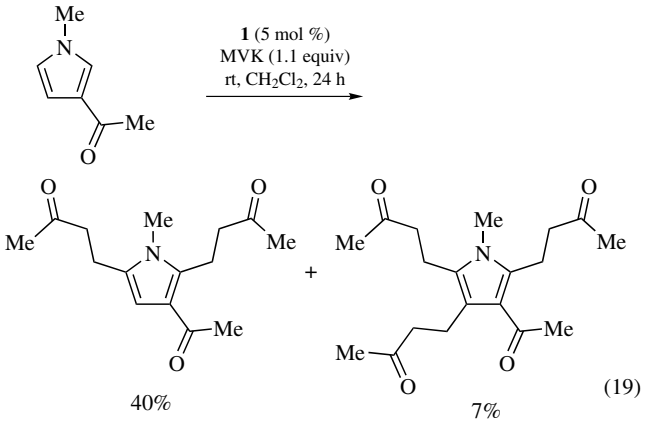
(17)

As Oxophilic Lewis Acid. In search for Lewis acids of mild acidity and devoid of nucleophilic anion, Yu and coworkers found that $Ph_3PAuOTf$ offered the best results in the glycosidation of 1,2-anhydrosugars, increasing yields by >20% compared to the conventional protocol based on superstoichiometric anhydrous $ZnCl_2$.[30] Complex **1** was less efficient (eq 18).



1 (10 mol %), CH_2Cl_2/THF (3:2)	78%	(18)
$Ph_3PAuOTf$ (20 mol %), CH_2Cl_2	88%	

In Hashmi's study of hydroarylations with pyrroles,[31] multiple substitutions were observed using **1** as well as $AgPF_6$ and TsOH. Likely, complex **1** was acting as a Lewis acid activating the methyl vinyl ketone (eq 19).



(19)

1. Mezailles, N.; Ricard, L.; Gagosz, F., *Org. Lett.* **2005**, *7*, 4133.
2. Hashmi, A. S. K., *Chem. Rev.* **2007**, *107*, 3180.
3. Fürstner, A.; Davis, P. W., *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.
4. Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M., *Angew. Chem., Int. Ed.* **2004**, *43*, 2402.
5. Rautenstrauch, V., *J. Org. Chem.* **1984**, *49*, 950.
6. Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M., *J. Am. Chem. Soc.* **2005**, *127*, 6178.
7. Staben, S. T.; Kennedy-Smith, J. J.; Tosie, F. D., *Angew. Chem., Int. Ed.* **2004**, *43*, 5350.
8. Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D., *Angew. Chem., Int. Ed.* **2004**, *43*, 5350.
9. Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D., *J. Am. Chem. Soc.* **2004**, *126*, 4526.
10. Sherry, B. D.; Toste, F. D., *J. Am. Chem. Soc.* **2004**, *126*, 15978.
11. Luzung, M. R.; Markham, J. P.; Toste, F. D., *J. Am. Chem. Soc.* **2004**, *126*, 10858.
12. Nevado, C.; Echavarren, A. M., *Chem. Eur. J.* **2005**, *11*, 3155.
13. Munoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M., *Organometallics* **2005**, *24*, 1293.
14. Lemiere, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M., *Angew. Chem., Int. Ed.* **2006**, *45*, 7596.
15. Zhang, L., *J. Am. Chem. Soc.* **2005**, *127*, 16804.
16. Yu, M.; Li, G.; Wang, S.; Zhang, L., *Adv. Synth. Catal.* **2007**, *349*, 871.
17. Yu, M.; Zhang, G.; Zhang, L., *Org. Lett.* **2007**, *9*, 2147.
18. Buzas, A.; Istrate, F.; Gagosz, F., *Org. Lett.* **2006**, *8*, 1957.
19. Buzas, A.; Gagosz, F., *Org. Lett.* **2006**, *8*, 515.
20. Kang, J.-E.; Shin, S., *Synlett* **2006**, 717.
21. Buzas, A.; Gagosz, F., *Synlett* **2006**, 2727.
22. Miyabe, H.; Sami, Y.; Naito, T.; Takemoto, Y., *Heterocycles* **2007**, *73*, 187.
23. Hashmi, A. S. K.; Salathe, R.; Frey, W., *Synlett* **2007**, 1763.
24. Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W., *Eur. J. Org. Chem.* **2006**, 4905.
25. Istrate, F. M.; Gagosz, F., *Org. Lett.* **2007**, *9*, 3181.
26. Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y., *J. Org. Chem.* **2007**, *72*, 4462.
27. Enomoto, T.; Obika, S.; Yasui, Y.; Takemoto, Y., *Synlett* **2008**, 1647.
28. Obika, S.; Yasui, Y.; Yanada, R.; Takemoto, Y., *J. Org. Chem.* **2008**, *73*, 5206.
29. Brouwer, C.; Rahaman, R.; He, C., *Synlett* **2007**, 1785.
30. Li, Y.; Tang, P.; Chen, Y.; Yu, B., *J. Org. Chem.* **2008**, *73*, 4323.
31. Hashmi, A. S. K.; Salathe, R.; Frey, W., *Eur. J. Org. Chem.* **2007**, 1648.

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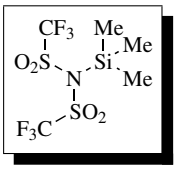
1,1,1-Trifluoro-*N*-[(trifluoromethyl)-sulfonyl]-*N*-(trimethylsilyl)methane-sulfonamide



[82113-66-4] $C_5H_9F_6NO_4S_2Si$ (MW 353.34)
InChI = 1/C5H9F6NO4S2Si/c1-19(2,3)12(17(13,14)4(6,7)8)18(15,16)5(9,10)11/h1-3H3
InChIKey = MLIRNWUYOYIGBZ-UHFFFAOYAW

(Lewis acid catalyst for a variety of organic transformations)

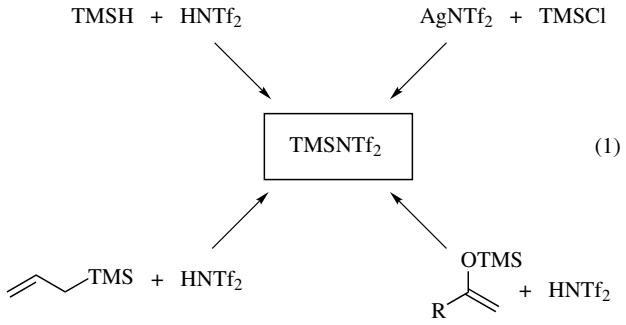
Alternate Names: $TMSNTf_2$.
Physical Data: colorless liquid, bp: 115 °C (2 Torr).
Solubility: soluble in most common organic solvents, commonly used in dichloromethane, toluene, diethyl ether.

Form Supplied in: not commercially available.

Preparative Methods: easily prepared in situ through protodesilation by mixing commercially available allyltrimethylsilane (or any TMS enol ether) and Tf_2NH. Originally prepared by mixing Tf_2NH with trimethylsilane at low temperature or mixing $AgNTf_2$ with TMSCl.

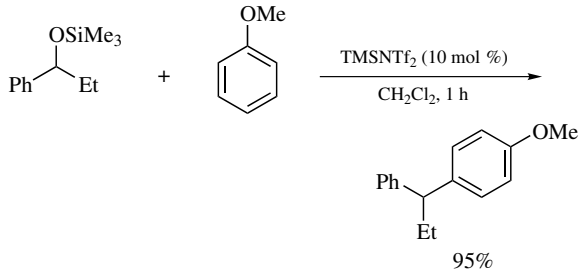
Handling, Storage, and Precautions: flammable, corrosive, very hygroscopic.

Synthesis. The original synthesis of $TMSNTf_2$ by DesMarteau involved mixing of Tf_2NH and TMSH, liberating H_2.[1] Schreeve then used metathesis with $AgNTf_2$ and TMSCl to generate $TMSNTf_2$.[2] Currently, $TMSNTf_2$ is commonly prepared in situ by mixing allyl-TMS and TMS-enol ethers or TMS-ketene acetals in a 1:1 ratio with the commercially available Tf_2NH (eq 1).[3]



(1)

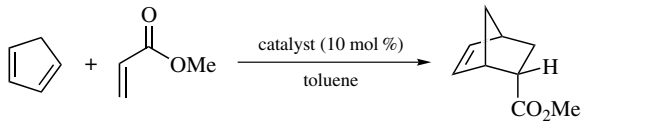
Friedel–Crafts Alkylation. One of the first uses for this highly Lewis acidic reagent in organic synthesis was found by Mikami in the Friedel–Crafts alkylation reaction of anisole (eq 2).[4] Here the first example of $TMSNTf_2$ outperforming TMSOTf was found.



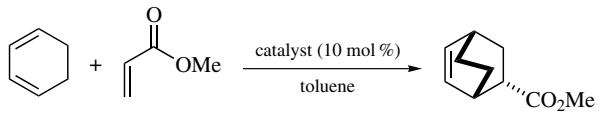
(2)

Cyclization Reactions. Ghosez further explored the reactivity of this reagent and realized success in the Diels–Alder reaction of cyclic and acyclic dienes (eq 3).[3,5] Although TfOH is reported to be a stronger Brønsted acid than Tf_2NH, $TMSNTf_2$ was found to have a higher Lewis acidity than TMSOTf and has since been found to promote a variety of reactions in which TMSOTf fails.

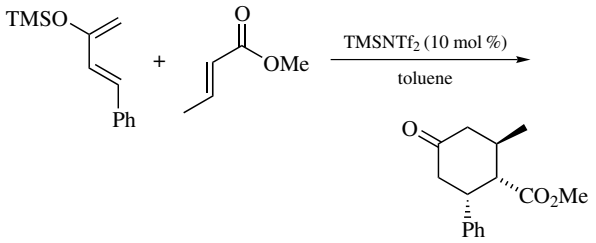
$TMSNTf_2$ [as well as other trialkylsilyl-bis(trifluoromethanesulfonyl)imides] was also found to promote a [2 + 2] cyclization of allylsilanes with acrylates (eq 4).[6] Acrylonitrile and methyl propiolate were found to be suitable [2 + 2] reaction partners. Many examples from this report use Tf_2NH as the catalyst initiator and with the common trend, TfOH was unable to promote this cyclization reaction.



$TMSNTf_2$: 83% yield, 24/1 *endo/exo*
TMSOTf: <5% yield, 13.3/1 *endo/exo*



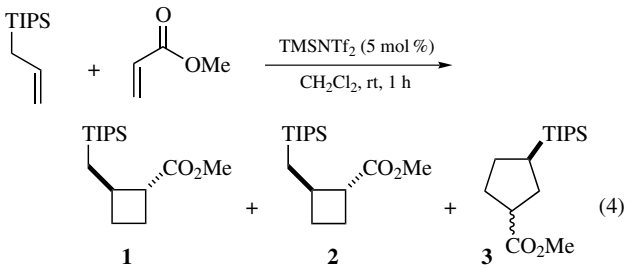
$TMSNTf_2$: 92% yield, 49/1 *endo/exo*
TMSOTf: nr



(3)

79% yield
9/1 *endo/exo*

Allylation. The use of allyl-TMS and Tf_2NH to generate $TMSNTf_2$ in situ has also been applied to the allylation reaction. Robertson reported the highly regioselective and diastereoselective Sakurai reaction to cyclopentenones (eq 5).[7] Again, $TMSNTf_2$ was required for reactivity whereas TfOH or standard conditions ($TiCl_4$, 24 h) gave no Sakurai product. This system was even able to promote the 1,4-addition to a less reactive α, β- unsaturated ester (eq 5).



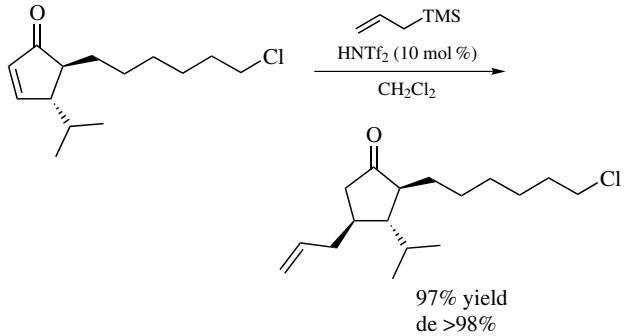
1 **2** **3**

(4)

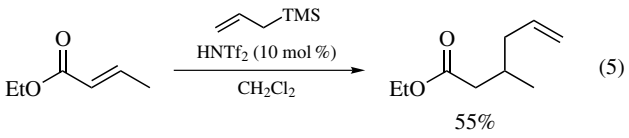
93%
75/8/17 (**1/2/3**)

The allylation of ketones and aldehydes was accomplished by Yamamoto,[8] where preformation of $TMSNTf_2$ was done in diethyl ether at −78 °C for 15 min. Slow addition of the carbonyl compound followed by acidic hydrolysis gave the allylation products in high yield (eq 6).

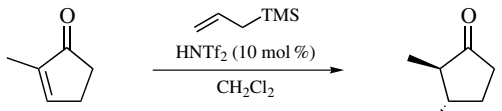
Aldol and Aldol-type Reactions. Yamamoto also used this procedure for the aldol reaction between TMS enol ethers with aldehydes and ketones (eq 7).[8]



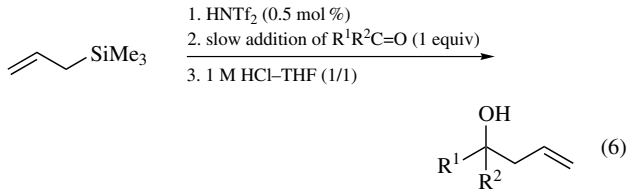
97% yield
de >98%



55% (5)



95%



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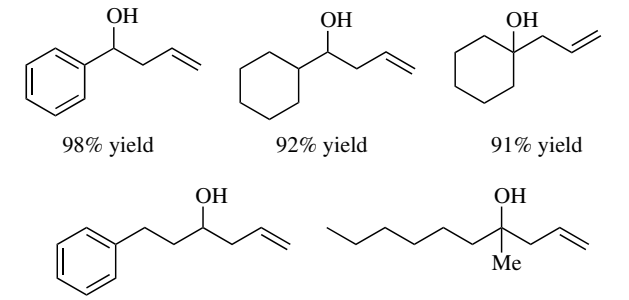
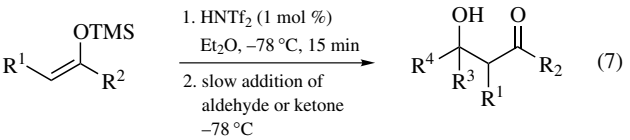


98% yield 92% yield 91% yield

90% yield 89% yield



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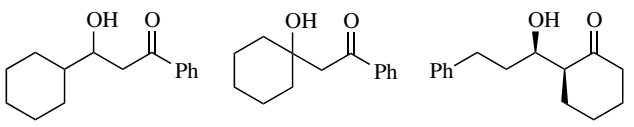
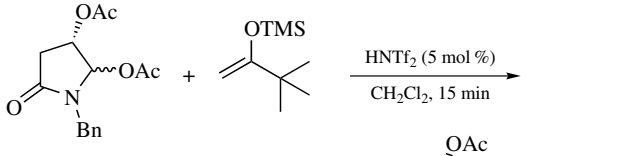
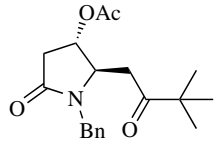


87% 87% 92%
70/30 *syn/anti*

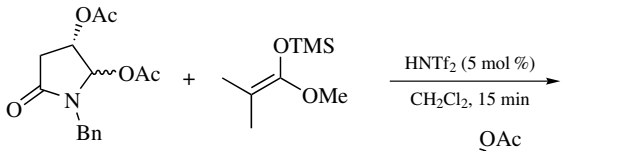
The use of TMS-enol ethers, and -ketene acetals with the $TMSNTf_2$ catalyst was also shown to be quite effective for the α-amido alkylation (eq 8).[9] High diastereoselectivty was obtained in many cases, whereas TfOH was again unable to promote the reaction.

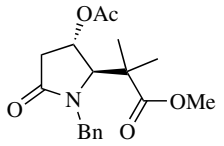




(8)

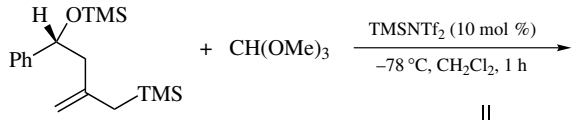
90%
95/5 *trans/cis*

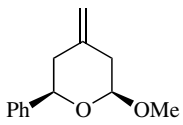




86%
99/1 *trans/cis*

Tetrahydropyran Formation. The use of an appropriately substituted allylsilane with a variety of electrophiles with 10% $TMSNTf_2$ gave the cyclized tetrahydropyran compounds (eq 9). For this reaction, $TMSNTf_2$ *outperformed* a variety of Lewis acids including: TMSOTf, $TiCl_4$, $TiCl_2(Oi\text{-}Pr)_2$, $SnCl_4$, $BF_3{\cdot}OEt_2$, and $EtAlCl_2$.[10]





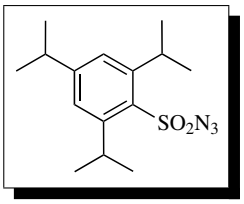
(9)

83%
dr 11:1

1. Foropoulos, J.; Jr, DesMarteau, D. D., *Inorg. Chem.* **1984**, *23*, 3720.
2. Vij, A.; Zheng, Y. Y.; Kirchmeier, R. L.; Shreeve, J. M., *Inorg. Chem.* **1994**, *33*, 3281.
3. Mathieu, B.; Ghosez, L., *Tetrahedron* **2002**, *58*, 8219.
4. Ishii, A.; Kotera, O.; Saeki, T.; Mikami, K., *Synlett* **1997**, 1145.
5. Mathieu, B.; Ghosez, L., *Tetrahedron Lett.* **1997**, *38*, 5497.
6. Takasu, K.; Hosokawa, N.; Inanaga, K.; Ihara, M., *Tetrahedron Lett.* **2006**, *47*, 6053.
7. Kuhnert, N.; Peverley, J.; Robertson, J., *Tetrahedron Lett.* **1998**, *39*, 3215.
8. Ishihara, K.; Hiraiwa, Y.; Yamamoto, H., *Synlett* **2001**, 1851.
9. Othman, R. B.; Bousquet, T.; Othman, M.; Dalla, V., *Org. Lett.* **2005**, *7*, 5335.
10. Yu, C.-M.; Lee, J.-Y.; So, B.; Hong, J., *Angew. Chem., Int. Ed.* **2002**, *41*, 161.

Matthew B. Boxer
University of Chicago, Chicago, IL, USA

2,4,6-Triisopropylbenzenesulfonyl Azide[1]



[36982-84-0] $C_{15}H_{23}N_3O_2S$ (MW 309.48)

InChI = 1/C15H23N3O2S/c1-9(2)12-7-13(10(3)4)15(14(8-12)11(5)6)21(19,20)18-17-16/h7-11H,1-6H3

InChIKey = AEMWUHCKKDPRSK-UHFFFAOYAB

(agent for diazo[2] and azide[3] transfer to enolates)

Alternate Name: trisyl azide.

Physical Data: mp 41–43 °C.

Solubility: freely sol most organic solvents.

Preparative Methods: readily prepared by treatment of the commercially available triisopropylbenzenesulfonyl chloride (trisyl chloride) with sodium azide.[4]

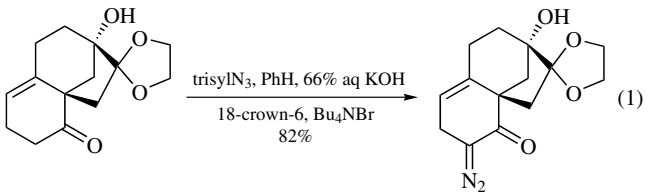
Original Commentary

Lewis N. Mander

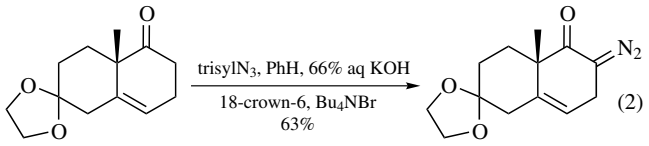
The Australian National University, Canberra, Australian Capital Territory, Australia

General Considerations. The reactions of arylsulfonyl azides with enolates have been reported to give a range of products, depending on the fragmentation of the initial adduct.[3,5] This may differ according to the nature of the enolate, the particular sulfonyl azide, and the quenching procedure. Net diazo transfer is usually observed for stabilized enolates, while azide transfer is more common with more reactive enolates.

Diazo Transfer to Ketones. Triisopropylbenzenesulfonyl azide has been used for the direct transfer of the diazo group to ketone enolates under phase transfer conditions to furnish α-diazo ketones (eqs 1–4).[2,6–8]

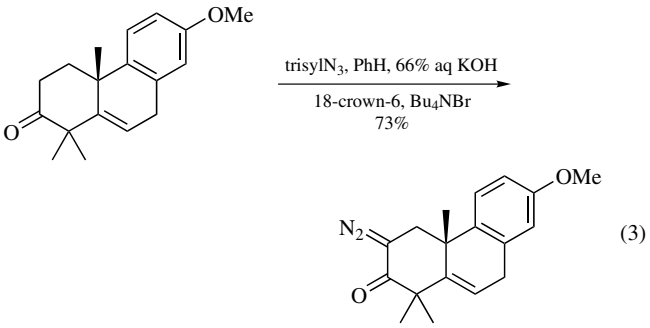


(1)

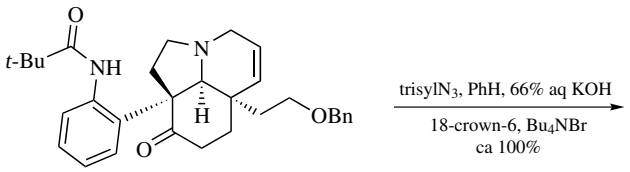


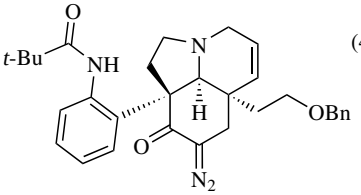
(2)

The method may be used as a more direct alternative to the stepwise procedure of hydroxymethylenation, followed by treatment with *p*-toluenesulfonyl azide and triethylamine,[9] but its greatest value lies with the reactions of sterically hindered substrates (eqs 5–9),[2,10–12] for which the two-stage process is ineffective. The utility of the trisyl azide in these conversions stems from the steric hindrance afforded by the *ortho* isopropyl groups; simpler arylsulfonyl azides are degraded too rapidly under these conditions to be useful. The method appears to be less effective with cyclopentanones (eq 9)[13] and several failures have been reported with such substrates.[14]



(3)





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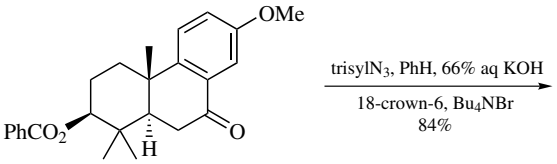

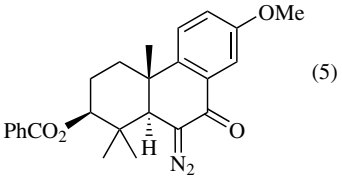

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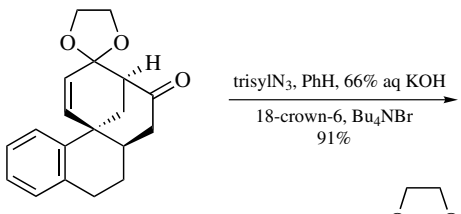

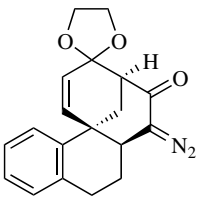

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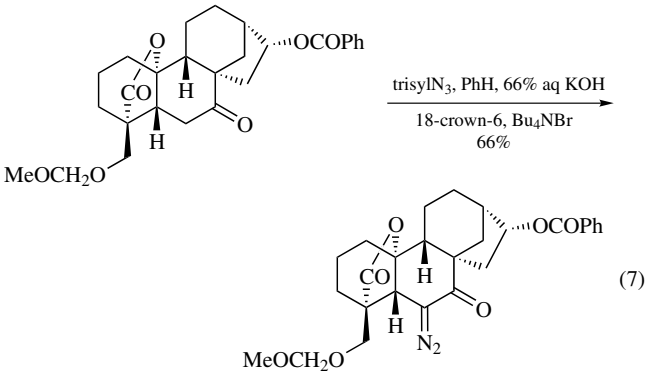

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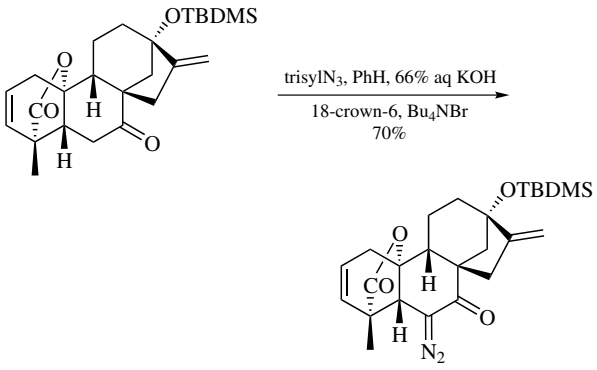

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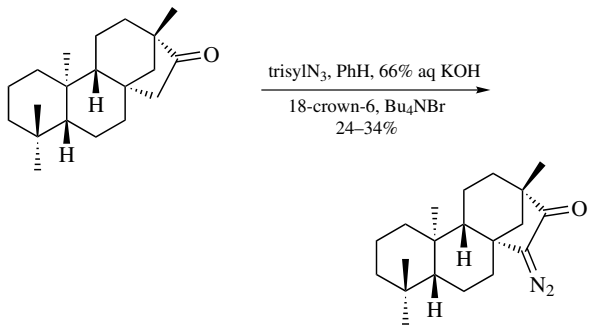
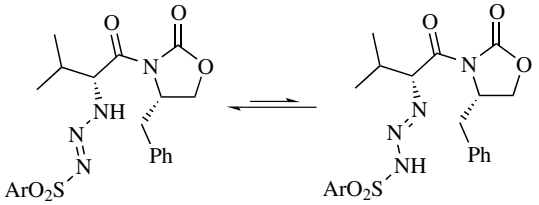


(9)

Azide Transfer to Enolates. Kinetically controlled azide transfer to the lithium enolates of azetidinones was originally demonstrated with tosyl azide using chlorotrimethylsilane as a quenching reagent,[15] but was found not to be general for other enolates. One of the problems is competing diazo transfer. In a systematic study of azide transfer to imide enolates,[5] it was found that azide transfer is more strongly favored by more electropositive counterions (K > Na ≫ Li), and by more electron-rich arylsulfonyl azides (trisyl > tosyl > *p*-nitrobenzenesulfonyl). The steric requirements of the trisyl group undoubtedly play a role also. Triazenes are implicated as intermediates and it is the treatment of these compounds which determines the product distribution rather than the initial step. Triazene (**1**) was sufficiently stable to be isolated as a mixture of tautomers and it was found that decomposition to azide (**2**) could be effected with potassium acetate, but not lithium acetate. Thus the counterion effect noted above is expressed in triazene decomposition, rather than the initial addition of the enolate to the azide.



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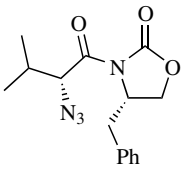
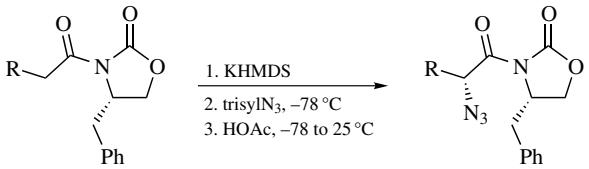


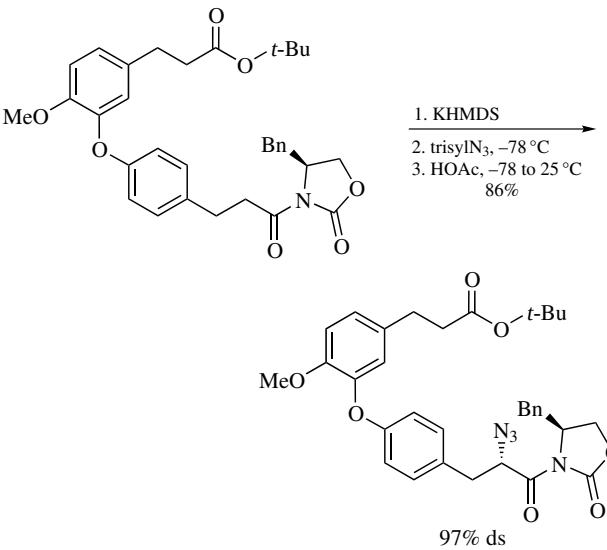
(2)

The most general protocol (eq 10) has therefore been based on potassium hexamethyldisilazide (KHMDS) as the base, addition of trisyl azide at −78 °C and then acetic acid at the same temperature.[5] Excellent levels of diastereoselectivity are observed with most substrates and the method has been used widely in the enantioselective synthesis of α-amino acids from chiral imides.[16] Chemoselective azidation of an imide enolate in the presence of an ester function has been demonstrated (eq 11).[17] The product distribution is nevertheless finely balanced, as discovered with the respective dimethyl and dibenzyl ethers of the 3,5-substituted phenylacetyl imide (**3**) (eq 12).[18]



(10)

R = CH_2Ph ds = 97% (91% yield)
R = Me ds = 97% (74% yield)
R = Ph ds = 91% (82% yield)
R = *t*-Bu ds = 99% (90% yield)

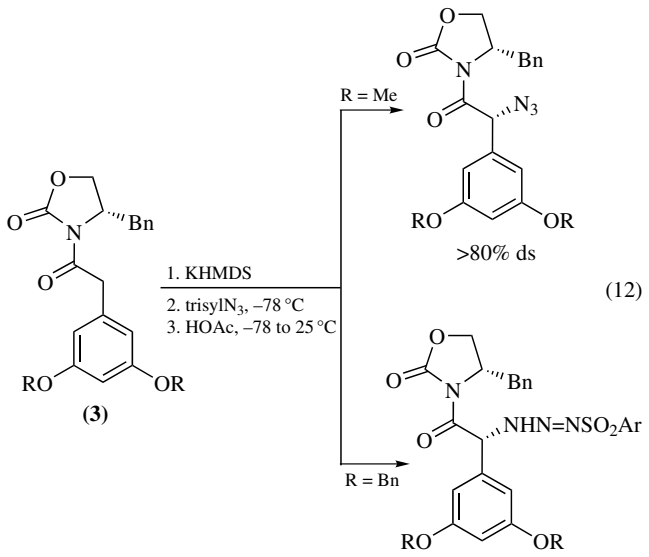


(11)

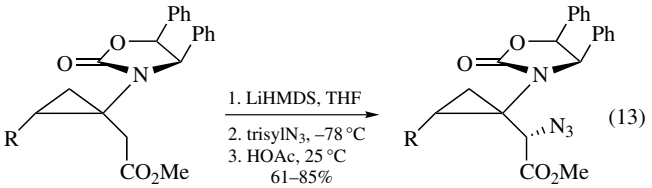
97% ds

The azide transfer methodology may also be applied to a variety of esters[19] and is compatible with a number of other functional groups (eqs 13–15).[20,21] It may also be used with

phosphonates (eq 16),[22] and if the counterion to the anion is lithium, as in the earlier imide study, it is possible to isolate the simple adduct retaining the sulfonyltriazine moiety (eq 17). Reaction with an *N*-hydroxy β-lactam afforded the deoxy-α-azido lactam via the *O*-sulfonate.[23]

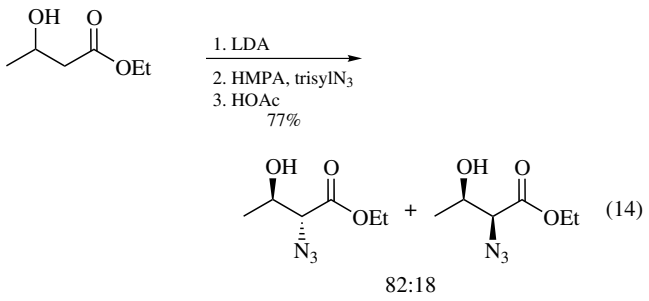


(12)

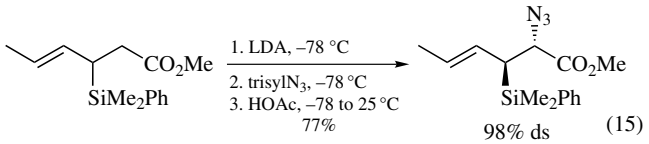


(13)

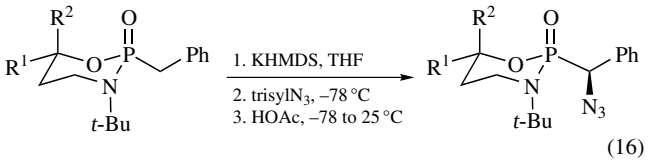
R = Me, Et, CH_2OMe, CH_2OBn



(14)

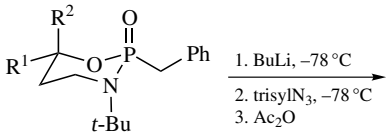


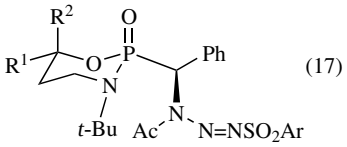
(15)



(16)

R^1, R^2 = Me; >95% ds (52–68% yield)
R^1 = Me, R^2 = H; 57% ds (52–70% yield)





(17)

R^1, R^2 = Me; >95% ds (70–93% yield)
R^1 = Me, R^2 = H; 92% ds (75% yield)

First Update

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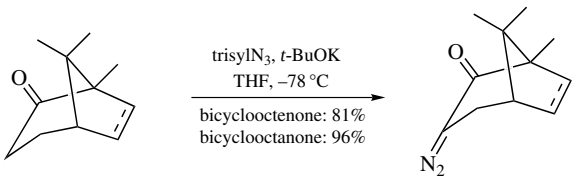
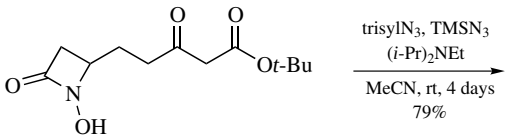
Diazo Transfer to Ketones. In the synthesis of α-diazo bicyclo[3.2.1]octenone and octanone, Uyehara and coworkers[25] found that the direct diazo-transfer reaction under homogeneous conditions composed of *t*-BuOK in THF was much more reliable, reproducible, and high yielding than the original Mander phase-transfer conditions (eq 18).[2]

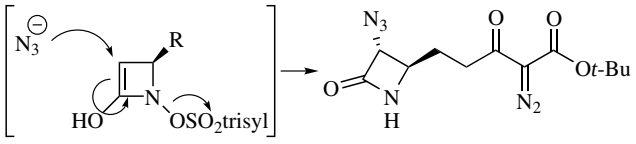


(18)

Miller and coworkers discovered an interesting transformation of β-ketoester containing *N*-hydroxy β-lactam with a mixture of trisyl azide and trimethylsilyl azide (eq 19).[26] The anticipated formation of α-diazo β-ketoester proceeded smoothly. However, the cleavage of the N–O bond and the concurrent azidation of β-lactam were not anticipated. The authors suggest that α-azido β-lactam is formed via the sulfonylation of *N*-hydroxy β-lactam with trisyl azide and trimethylsilyl azide followed by an S_N2'-displacement of allylic trisylsulfonate with an azide. Hunig's base and the additional trimethylsilyl azide are key to obtaining high overall yield for these three remarkable transformations in one step.

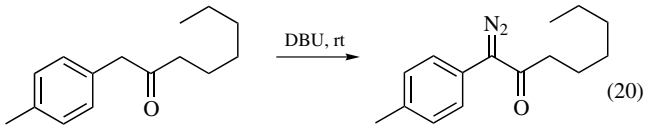


(19)



Recently, Taber and Tian had pointed out a significant improvement in the isolated yield of the α-diazo *p*-tolyloctanone when

trisyl azide was employed in the diazo-transfer reaction (eq 20).[27] Thus, trisyl azide (entry 5) was superior compared to mesyl azide (entry 1), 4-nitrobenzenesulfonyl azide (entry 2), benzenesulfonyl azide (entry 3), and 4-acetylbenzenesulfonyl azide (entry 4). Further optimization efforts revealed that an equal molar equivalent of α-aryl ketone and trisyl azide with 3 equiv of DBU in toluene at room temperature provided an 80% yield of the desired α-diazo ketone (entry 7 vs. entries 5 and 6).

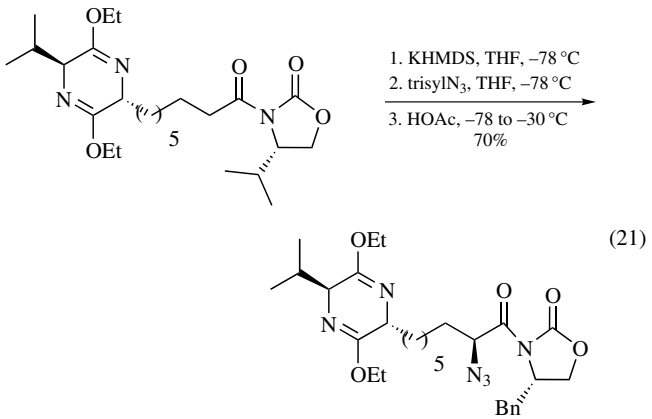


(20)

Entry	Azide reagent	Equiv	DBU (equiv)	Solvent	Time (h)	Yield (%)
1	Mesyl azide	3	3	CH_2Cl_2	3	13
2	PNBSA[a]	3	3	CH_3CN	8	15
3	BSA[b]	1.2	1.5	CH_3CN	0.5	26
4	AABSA[c]	2	1.5	CH_3CN	1	38
5	Trisyl azide	1.0	1.2	CH_3CN	2	53
6	Trisyl azide	1.1	1.4	Toluene	3	68
7	Trisyl azide	1.0	3	Toluene	3	80

[a]4-Nitrobenzenesulfonyl azide.
[b]Benzenesulfonyl azide.
[c]4-Acetylbenzenesulfonyl azide.

Azide Transfer to Enolates. Evans' chiral oxazolidinone auxiliaries continue to be widely used in the azide transfer to enolates because high stereoselectivity can be achieved (eqs 21,[28] 22,[29] and 23[30]).



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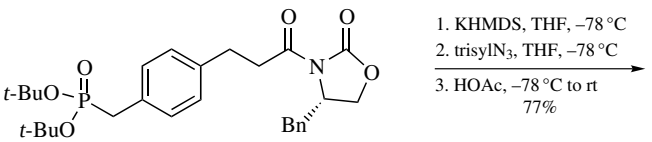

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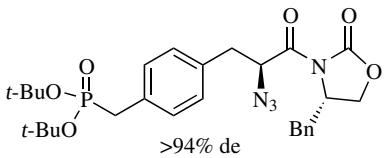

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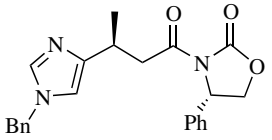
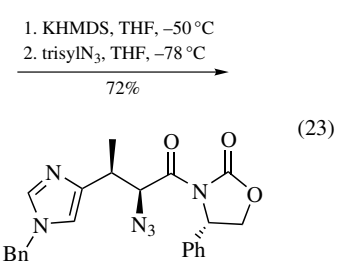
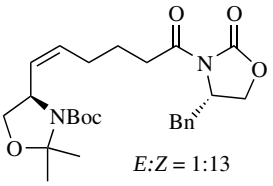
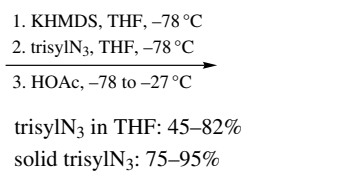


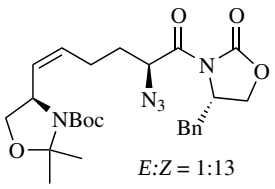


(23)

Interestingly, Holmes and coworkers found that a complete conversion of starting materials and good to excellent isolated yield of the azidation product could be obtained when solid trisyl azide rather than a solution of trisyl azide in THF was used (eq 24).[31] This synthetic modification could be of tremendous help for chemists.

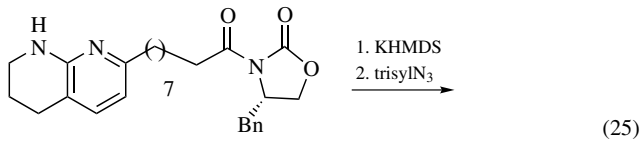




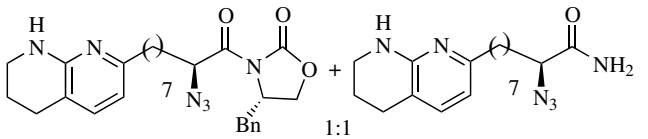


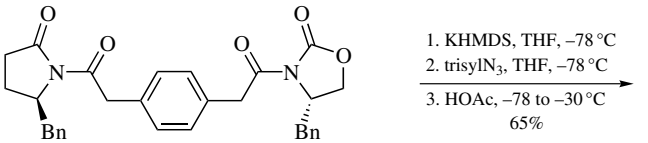
(24)

Under similar azide transfer to enolate conditions, the unexpected primary amide that arose from the hydrolysis of the Evans' chiral auxiliary was also isolated (eq 25).[32] Double enolization of the bisamide followed by trapping of the dianion with trisyl azide provided the diazido diastereoisomers in 4:1 ratio (eq 26).[33]

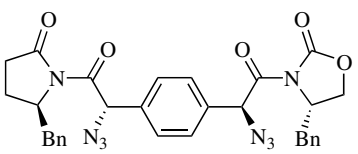


(25)



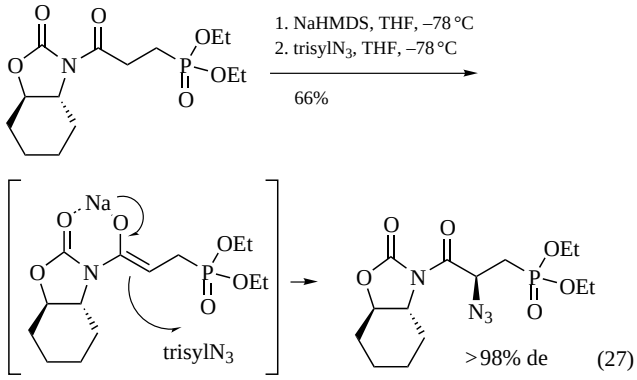


(26)



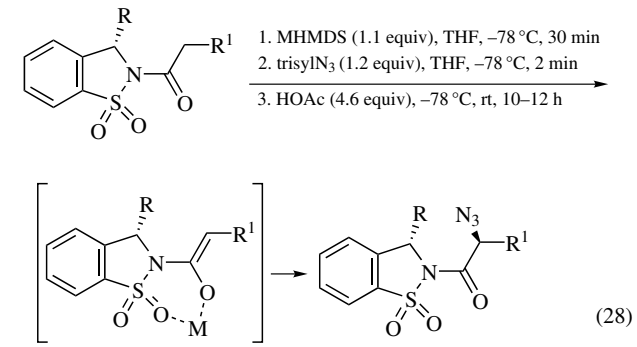
α,α'-diazido isomers
(*S*,*S*):(*R*,*S*) 4:1

Hexahydrobenzooxazolidinone chiral auxiliary also provided an azidation product with high diastereoselectivity (eq 27).[34] This chiral auxiliary can be removed with $LiOH/H_2O_2$.



(27)

Beside chiral oxazolidinone auxiliaries, chiral sultams have also been investigated. A chiral benzosultam could effect the asymmetric azidation with high stereoselectivity (eq 28).[35] The diastereoselectivity increases with the more sterically demanding R-substitutent. For example, the *tert*-butyl group provides a >98:2 diastereoselectivity ratio (dr) and the highest isolated yield (entry 3 vs. entries 1 and 2). Interestingly, KHMDS gave a lower diastereoselectivity and yield than NaHMDS when R^1 was an allylic group (entry 4 vs. entry 3). However, the diastereoselectivity was similar regardless of the base when R^1 was a benzylic group (entry 5 vs. entry 6). The stereoselectivity could arise from a more stable (*Z*)-enolate chelating to the sultam oxygen that reacted with trisyl azide on the opposite face of the R-substitutent. The benzosultam auxiliary can be hydrolyzed with $LiOH/H_2O_2$ to liberate the chiral α-azido acid.

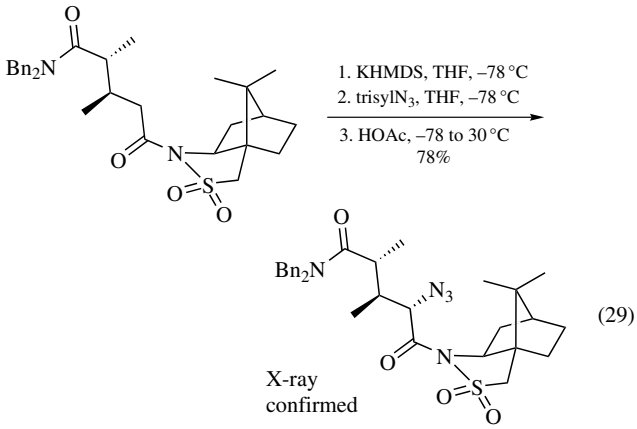


(28)

Entry	R	R^1	M	% Yield	dr[a]
1	Me	$CH_3CH=CH_2$	Na	72	95:5
2	*i*-Pr	$CH_2CH=CH_2$	Na	73	95:5
3	*t*-Bu	$CH_2CH=CH_2$	Na	96	>98:2
4	*t*-Bu	$CH_2CH=CH_2$	K	63	93:7
5	*t*-Bu	CH_2Ph	Na	85	99:1
6	*t*-Bu	CH_2Ph	K	79	>98:2

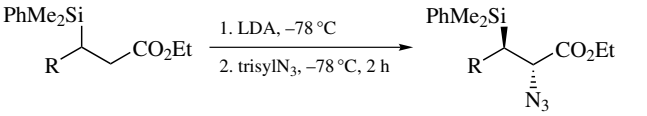
[a]Determined by ^1H NMR analysis.

Joullié and coworkers utilized camphorsultam in the synthesis of glutamine derivatives (eq 29).[36] The camphorsultam auxiliary could be cleaved with lithium hydroxide.



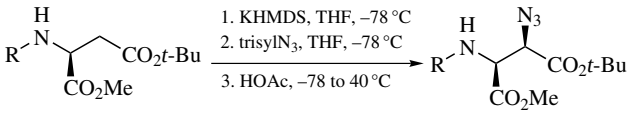
(29)

Besides the oxazolidinones and sultams, esters also participated in the azidation reaction. For example, electrophilic azidation of β-silyl ester enolate with trisyl azide provided mainly the *anti*-β-silyl azide (eq 30).[21,37] Introduction of the azide into aspartate derivatives provided precursors to 2,3-diaminosuccinic acid (eq 31).[38] This reaction gave a single diastereomer in moderate yield.



R = Ph, 64%; *anti/syn* > 98:2
R = Me, 58%; *anti/syn* > 98:2

(30)



R = Alloc, 50%
R = Boc, 54%

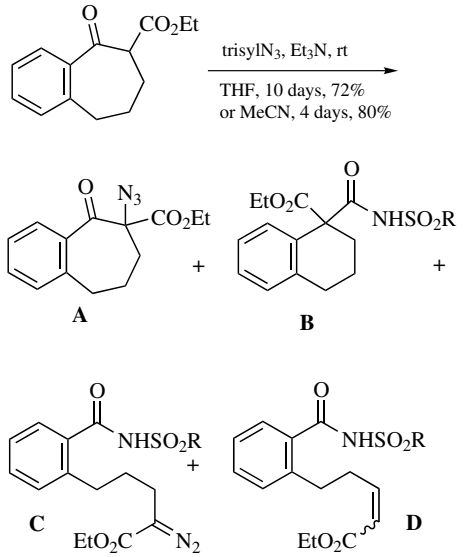
(31)

Another advantage of sterically demanding trisyl azide is the selective azidation of cyclic β-ketoesters (eq 32).[39] Thus, the desired azidation product **A** was slowly formed as a single product in either THF or MeCN. In contrast, more reactive sulfonyl azides such as 4-methoxybenzenesulfonyl azide, 4-nitrobenzenesulfonyl azide, mesyl azide, triflyl azide, and tosyl azide provided not only the azidation product **A** but also a ring-contraction product **B**, a ring-opened diazo-transfer product **C**, and a mixture of ring-opened olefins **D**. The amounts of by-products **B**, **C**, and **D** were dependent upon the azide reagent.

Hanessian and coworkers took advantage of azidation to introduce an amino group into an indolizidinone ring system (eq 33).[40] The reaction proceeded with moderate yield presumably due to a lower reactivity of the generated enolate to give a 2:1 mixture of diastereomers. The trisyl azide reacted preferentially on the *endo*-face of the indolizidine ring system on the opposite side of the bulky silyl protecting group.

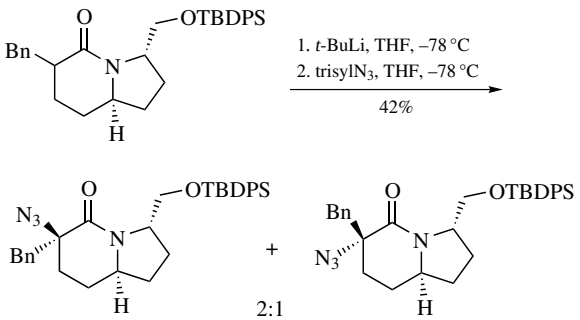
For lactones, Shiro and coworkers found that LiHMDS was superior compared to NaHMDS and KHMDS, providing the best yield of the desired azidation products, albeit with lower stereoselectivity (eq 34, entry 1 vs. entries 2 and 3).[41] Further optimization efforts revealed that TBDPS protecting group and TMSCl

quenching reagent provided the best overall yield of both diastereomers (entry 4).



(32)

R = 4-MeO-C_6H_4; Me; CF_3; 4-Me-C_6H_4; 4-NO_2-C_6H_4



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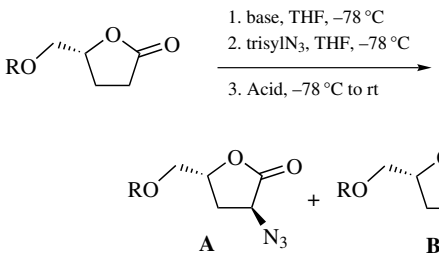
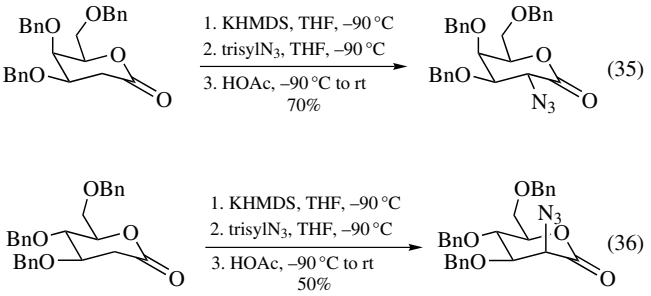


(34)

Entry	R	Base	Acid	Product (% yield)	
1	Tr	LiHMDS	AcOH	**A** (37%)	**B** (12%)
2	Tr	NaHMDS	AcOH	**A** (25%)	**B** (trace)
3	Tr	KHMDS	AcOH	**A** (11%)	**B** (trace)
4	TBDPS	LiHMDS	TMSCI	**A** (54%)	**B** (28%)

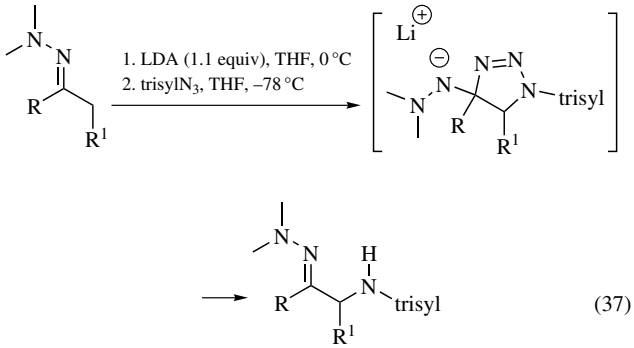
Trisyl azide was also successfully employed in the stereoselective electrophilic azidation of sugars (eqs 35 and 36).[42] The corresponding 2-azido epimer was not detected in either example. These 2-azido sugars were subsequently transformed into 2-amino sugars.



(35)

(36)

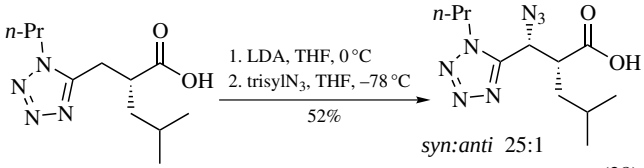
Enolates reacted with trisyl azide to produce α-azido keto species; however, azaenolates that originated from *N*,*N*-dimethyl hydrazones underwent an interesting [3 + 2]-cycloaddition with trisyl azide followed by a cycloreversion to provide α-sulfonamidohydrazones (eq 37).[43]



(37)

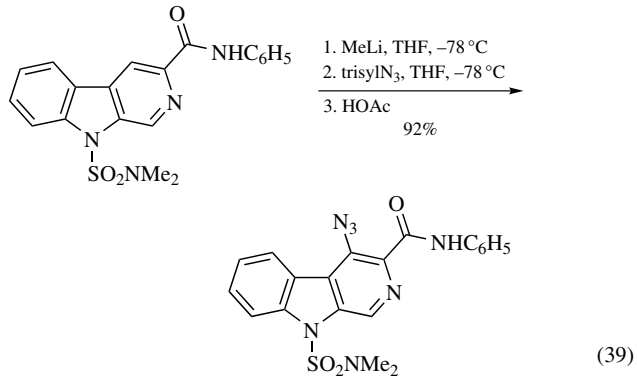
R	R^1	Yield (%)
Et	Me	84
n-Pr	Et	78
–$(CH_2)_4$–		66
Ph	Me	69
Bn	Ph	65

Regioselective LDA deprotonation of β-tetrazolyl propionic acid followed by trapping of the resultant β-anion with trisyl azide gives β-azido β-tetrazolyl propionic acid with high diastereoselectivity (eq 38).[44]



(38)

Other Anions. Trisyl azide could be used to introduce an azide into an aromatic system. Thus, ortho-lithiation of β-carboline with MeLi followed by trapping the anion with trisyl azide gave azido β-carboline, a precursor to amino β-carboline (eq 39).[45] In a similar manner, 1,1′-diazidoferrocene was prepared from ferrocene dianion and trisyl azide (eq 40).[46]



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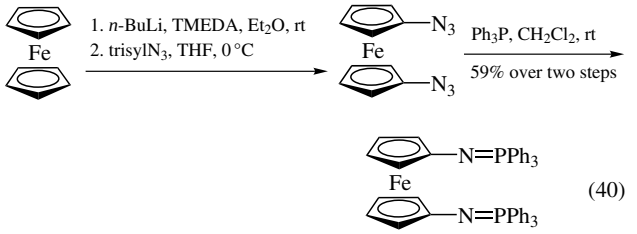
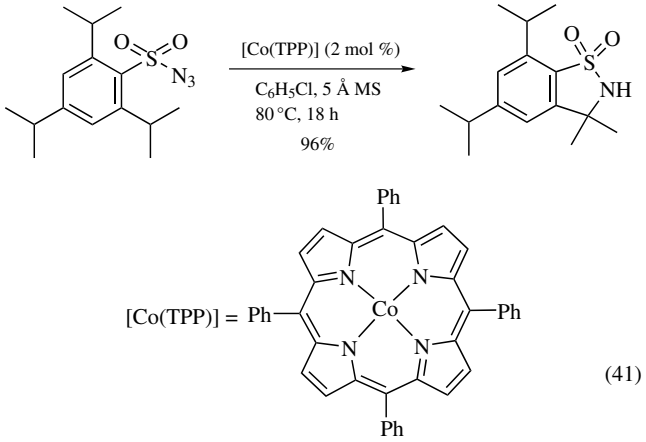


(40)

Miscellaneous. Trisyl azide itself underwent an intramolecular C–H amination in the presence of a catalytic amount of cobalt porphyrin complex to give the corresponding benzosultam (eq 41).[47]



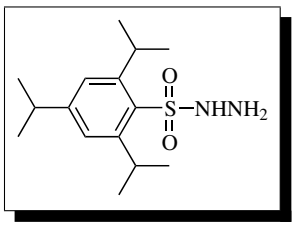
(41)

Related Reagents. *p*-toluenesulfonyl azide and methanesulfonyl azide have been used widely for diazo transfer to stabilized enolates.[9] The latter reagent simplifies isolation of the desired product,[24] but is potentially explosive and must be handled with care. Relative to other aryl analogs, the electron-deficient *p*-nitrobenzenesulfonyl analog favors diazo transfer to imide enolates.[5]

1. Harmon, R. E.; Wellman, G.; Gupta, S. K., *J. Org. Chem.* **1973**, *38*, 11.
2. Lombardo, L.; Mander, L. N., *Synthesis* **1980**, *5*, 368.
3. Evans, D. A.; Britton, T. C., *J. Am. Chem. Soc.* **1987**, *109*, 6881.
4. Leffler, J. E.; Tsuno, Y., *J. Org. Chem.* **1962**, *28*, 902.
5. Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L., *J. Am. Chem. Soc.* **1990**, *112*, 4011.
6. Lombardo, L.; Mander, L. N.; Turner, J. V., *J. Am. Chem. Soc.* **1980**, *102*, 6626.
7. Overman, L. E.; Robertson, G. M.; Robichaud, A. J., *J. Am. Chem. Soc.* **1991**, *113*, 2598.
8. Taber, D. F.; Schuchardt, J. L., *Tetrahedron* **1987**, *43*, 5677.
9. (a) Regitz, M., *Synthesis* **1972**, 351. (b) Regitz, M.; Maas, G. *Diazo Compounds, Properties and Synthesis*; Academic: Orlando, 1986; Chapter 13.
10. Robichaud, A. J.; Meyers, A. I., *J. Org. Chem.* **1991**, *56*, 2607.
11. (a) Mander, L. N.; Pyne, S. G., *J. Am. Chem. Soc.* **1979**, *101*, 3373. (b) Mander, L. N.; Pyne, S. G., *Aust. J. Chem.* **1981**, *34*, 1899.
12. Nuyttens, F.; Appendino, G.; De Clercq, P. J., *Synlett* **1991**, 526.
13. Coates, R. M.; Kang, H.-Y., *J. Org. Chem.* **1987**, *52*, 2065.
14. (a) Adams, J. L.; Metcalf, B. W., *Tetrahedron Lett.* **1984**, *25*, 919. (b) Rao, V. B.; George, C. F.; Wolff, S.; Agosta, W. C., *J. Am. Chem. Soc.* **1985**, *107*, 5732. (c) Fessner, W.-D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H., *J. Am. Chem. Soc.* **1987**, *109*, 4626.
15. Kühlein, K.; Jensen, H., *Justus Liebigs Ann. Chem.* **1974**, 369.
16. (a) Parry, R. J.; Ju, S.; Baker, B. J., *J. Labelled Comp. Radiopharm.* **1991**, *29*, 633. (b) Shaw, A. N.; Dolle, R. E.; Kruse, L. I., *Tetrahedron Lett.* **1990**, *31*, 5081. (c) Boteju, L. W.; Wegner, K.; Hruby, V. J., *Tetrahedron Lett.* **1992**, *33*, 7491. (d) Chen, H. G.; Beylin, V. G.; Marlatt, M.; Leja, B.; Goel, O. P., *Tetrahedron Lett.* **1992**, *33*, 3293. (e) Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; DeVries, K. M., *Tetrahedron Lett.* **1992**, *33*, 1189. (f) Pearson, A. J.; Park, J. G., *J. Org. Chem.* **1992**, *57*, 1744. (g) Beylin, V. G.; Chen, H. G.; Dunbar, J.; Goel. O. P.; Harter, W.; Marlatt, M.; Topliss, J. G., *Tetrahedron Lett.* **1993**, *34*, 953. (h) Thompson, W. J.; Ghosh, A. K.; Holloway, M. K.; Lee, H. Y.; Munson, P. M.; Schwering, J. E.; Wai, J.; Darke, P. L.; Zugay, J.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S., *J. Am. Chem. Soc.* **1993**, *115*, 801.
17. Evans, D. A.; Ellman, J. A., *J. Am. Chem. Soc.* **1989**, *111*, 1063.
18. Stone, M. J.; Maplestone, R. A.; Rahman, S. K.; Williams, D. H., *Tetrahedron Lett.* **1991**, *32*, 2663.
19. Stone, M. J.; van Dyk, M. S.; Booth, P. M.; Williams, D. H., *J. Chem. Soc., Perkin Trans. 1* **1991**, 1629.
20. Es-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A. I.; de Meijere, A., *Synlett* **1992**, 962.
21. Panek, J. S.; Beresis, R.; Xu, F.; Yang, M., *J. Org. Chem.* **1991**, *56*, 7341.
22. Denmark, S. E. Chatani, N.; Pansare, S. V., *Tetrahedron* **1992**, *48*, 2191.
23. Gasparski, C. M.; Teng, M.; Miller, M. J., *J. Am. Chem. Soc.* **1992**, *114*, 2741.
24. Taber, D. F.; Ruckle, R. E. Jr.; Hennessy, M. J., *J. Org. Chem.* **1986**, *51*, 4077.
25. Uyehara, T.; Takehara, N.; Ueno, M.; Sato, T., *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2687.
26. Teng, M.; Gasparski, C. M.; Williams, M. A.; Miller, M. J., *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2431.
27. Taber, D. F.; Tian, W., *J. Org. Chem.* **2007**, *72*, 3207.
28. Andrews, M. J. I.; Tabor, A. B., *Tetrahedron Lett.* **1997**, *38*, 3063.
29. Burke, T. R.; Liu, D.-G.; Gao, Y., *J. Org. Chem.* **2000**, *65*, 6288.
30. Angione, M. C.; Miller, S. J., *Tetrahedron* **2006**, *62*, 5254.
31. (a) Derrer, S.; Davies, J. E.; Holmes, A. B., *J. Chem. Soc., Perkin Trans. 1* **2000**, 2943. (b) Derrer, S.; Davies, J. E.; Holmes, A. B., *J. Chem. Soc., Perkin Trans. 1* **2000**, 2957.
32. Whitman, D. B.; Askew, B. C.; Duong, L. T.; Fernandez-Metzler, C.; Halczenko, W.; Hartman, G. D.; Hutchinson, J. H.; Leu, C.-T.; Prueksaritanont, T.; Rodan, G. A.; Rodan, S. B.; Duggan, M. E., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4411.
33. Falck-Pedersen, M. L.; Undheim, K., *Tetrahedron* **1996**, *52*, 7761.
34. Reyes-Rangel, G.; Maranon, V.; Avila-Ortiz, C. G.; Anaya de Parrodi, C.; Quintero, L.; Juaristi, E., *Tetrahedron* **2006**, *62*, 8404.
35. Ahn, K. H.; Kim, S.-K.; Ham, C., *Tetrahedron Lett.* **1998**, *39*, 6321.
36. Liang, B.; Carroll, P. J.; Joullié, M. M., *Org. Lett.* **2000**, *2*, 4157.
37. Chabaud, L.; Landais, Y., *Tetrahedron Lett.* **2003**, *44*, 6995.

38. Riemer, C.; Bayer, T.; Schmitt, H.; Kessler, H., *J. Peptide Res.* **2004**, *63*, 196.
39. Benati, L.; Nanni, D.; Spagnolo, P., *J. Org. Chem.* **1999**, *64*, 5132.
40. Hanessian, S.; Sailes, H.; Munro, A.; Therrien, E., *J. Org. Chem.* **2003**, *68*, 7219.
41. Shiro, Y.; Kato, K.; Fujii, M.; Ida, Y.; Akita, H., *Tetrahedron* **2006**, *62*, 8687.
42. Kumar, J. S. D.; Dupradeau, F.-Y.; Strouse, M. J.; Phelps, M. E.; Toyokuni, T., *J. Org. Chem.* **2001**, *66*, 3220.
43. Enders, D.; Joseph, R.; Poiesz, C., *Tetrahedron* **1998**, *54*, 10069.
44. Yang, M. G.; Modi, D. P.; Wexler, R. R.; Olson, R. E., *Tetrahedron Lett.* **2004**, *45*, 111.
45. Batch, A.; Dodd, R. H., *J. Org. Chem.* **1998**, *63*, 872.
46. Tarraga, A.; Oton, F.; Espinosa, A.; Desamparados Velasco, M.; Molina, P.; Evans, D. J., *Chem. Commun.* **2004**, 458.
47. Ruppel, J. V.; Kamble, R. M.; Zhang, X. P., *Org. Lett.* **2007**, *9*, 4889.

2,4,6-Triisopropylbenzenesulfonyl Hydrazide[1]



[39085-59-1] $C_{15}H_{26}N_2O_2S$ (MW 298.50)

InChI = 1/C15H26N2O2S/c1-9(2)12-7-13(10(3)4)15(20(18,19)17-16)14(8-12)11(5)6/h7-11,17H,16H2,1-6H3

InChIKey = UGRVYFQFDZRNMQ-UHFFFAOYAD

(used as a diazene equivalent;[3] condensed with ketones and aldehydes to form hydrazones that can be converted into reactive intermediates such as diazoalkanes, carbenes,[13] carbenium ions, alkyllithiums,[9] or umpolung synthons)

Alternate Name: trisyl hydrazide; TPSH.

Physical Data: mp 121–122 °C (dec).

Solubility: sol virtually all ethereal, halogenated, protic, and aprotic solvents; insol water and hydrocarbon solvents.

Analysis of Reagent Purity: NMR, IR, TLC.

Preparative Methods: may be prepared in 96% yield by treating commercially available 2,4,6-triisopropylbenzenesulfonyl chloride[2] with hydrazine hydrate in THF,[3,4] being careful to keep the reaction and workup temperatures below or around 0 °C. The solid can be dried in vacuo over P_2O_5 for 24 h.

Handling, Storage, and Precautions: decomposes rapidly in solution at rt to diazene, particularly under basic or neutral conditions; acid retards this degradation significantly. It is stable in solid form at −20 °C for months and may be freed from acidic impurities as described in the literature.[3] 2,4,6-Triisopropylbenzenesulfonylhydrazide is a toxic, potentially flammable solid which should be handled with gloves under an inert atmosphere.

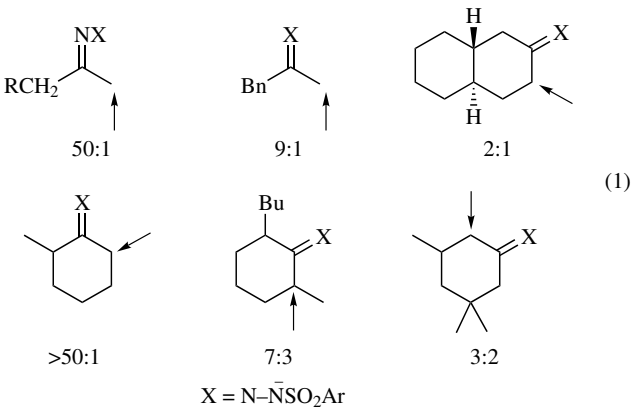
Original Commentary

A. Richard Chamberlin & James E. Sheppeck II
University of California, Irvine, CA, USA

Alkene Reduction. 2,4,6-Triisopropylbenzenesulfonyl hydrazide (TPSH) undergoes solvent-dependent thermal degradation into diazene (diimide) between 35 and 65 °C, resulting in the in situ reduction of alkenes and other double bonds in good to excellent yields.[3–6] TPSH remains one of the best sources of diazene, and addition of amine bases increases the rate of both diazene formation and hydrogenation. It is the most reactive of the common arenesulfonylhydrazides, being 380 and 24 times more reactive than *p*-toluenesulfonylhydrazide and mesitylenesulfonylhydrazide, respectively, under base-catalyzed conditions.[3]

Formation of Hydrazones. Much of the rich chemistry exhibited by TPSH comes from its condensation products with ketones and aldehydes. Such 'trisyl' hydrazones are typically prepared in excellent yield by mixing equimolar amounts of reagents in methanol or ethanol at room temperature with a catalytic amount of acid such as HCl and storing the reaction in the cold.[7] The product precipitates and is filtered off. Very hindered ketones such as camphor and diisopropyl ketone require stoichiometric amounts of acid and extraordinarily hindered ketones may not condense at all.[1,8]

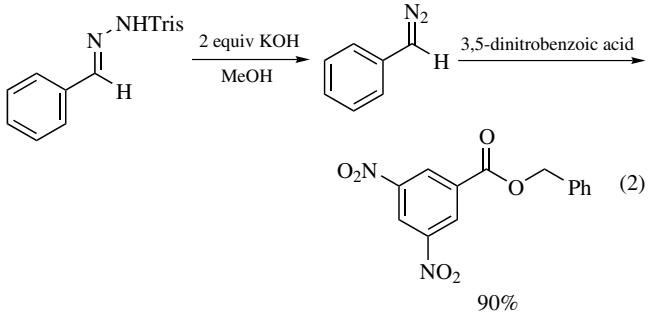
Electrophilic Additions to Hydrazone Anions. Trisylhydrazones can be quantitatively deprotonated with 2 equiv of butyllithium to give dianions which are highly nucleophilic and participate in alkylation, aldol, halogenation, and epoxide-opening reactions at low temperature.[9] Regioselectivity of deprotonation is dictated by three factors. First, and most important, is the geometry of the hydrazone C=N double bond, since the second equivalent of base is directed *syn* to the sulfonamide nitrogen anion in ethereal solvents.[10] Thus the mixture of azaenolates is determined by the ratio of isomeric hydrazones. TMEDA solvent negates the *syn*-directing effect and has been used extensively to deprotonate the less substituted α-carbon independent of hydrazone geometry.[11] Second, anion-stabilizing substituents in the α-position direct deprotonation. Third, is a general rule that methyl > methylene > methine in acidity. The preferred proton abstracted is illustrated with arrows in eq 1.[9d,12]



(1)

Bamford–Stevens and Shapiro Reactions. Thermal decomposition of the monoanions of arenesulfonylhydrazones in aprotic

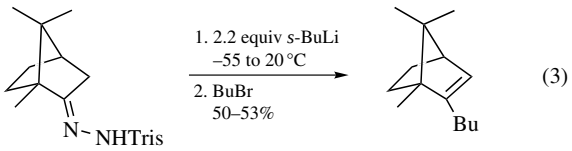
solvents such as glyme (the aprotic Bamford–Stevens reaction[13]) is a method of choice for forming diazo compounds and carbenes. Trisylhydrazones are well suited to this end and have been shown to be the superior reagent for diazoalkane formation in several instances (eq 2).[14]



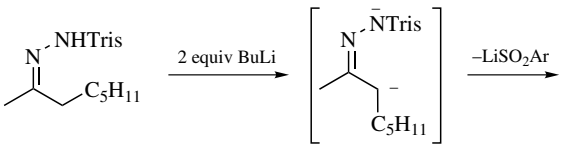
(2)

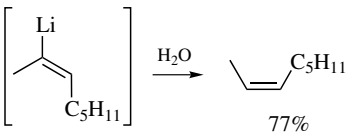
90%

Trisylhydrazones were originally investigated as an alternative to the shortcomings of tosylhydrazones in the Shapiro reaction.[12a] The former have the advantage that their anions decompose at lower temperatures and the bulky isopropyl substituents preclude *ortho* metalation, enabling the use of stoichiometric amounts of base. Acyclic azaenolates have a strong preference for $(E)_{CC}$ geometry[10] and undergo the Shapiro elimination to stereoselectively produce alkenes of (*Z*) geometry (eqs 3 and 4). The stereochemical fidelity of the azaenolate is compromised significantly, however, if there is hydrocarbon branching at the α'-center due to allylic strain.[1]



(3)

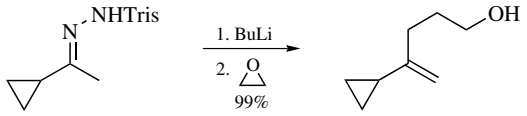




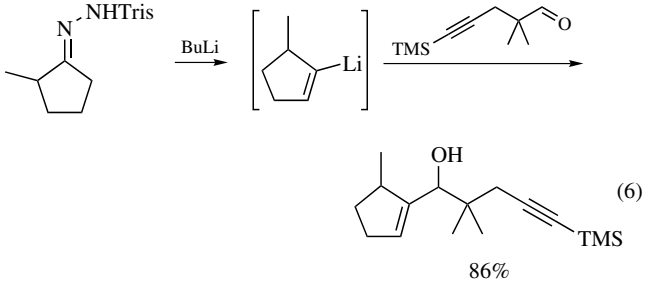
(4)

77%

The resulting vinyllithium intermediates may be trapped with a proton or some of the representative electrophiles shown in eqs 5–6.[11,15]



(5)

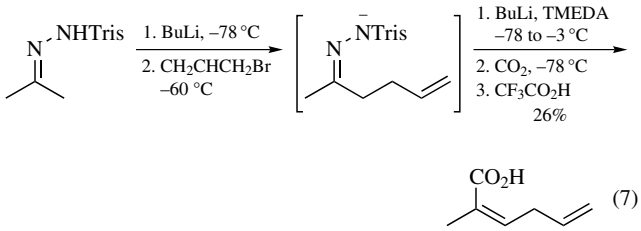


(6)

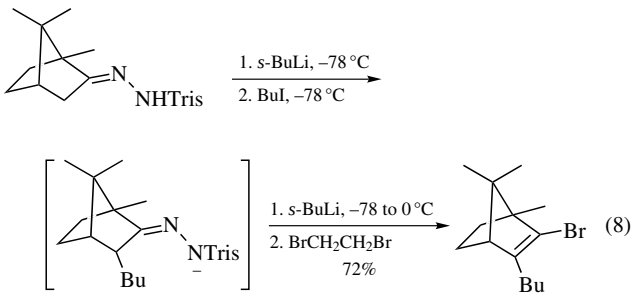
86%

Additional electrophiles include CO_2, DMF, formaldehyde, ethyl chloroformate, ketones, D_2O, halophosphines, halides, and propargylic tosylates.[9d,11,12a,16]

The Shapiro elimination also provides access to a diverse array of one-pot electrophile-substituted double bonds (eqs 7 and 8).[9]

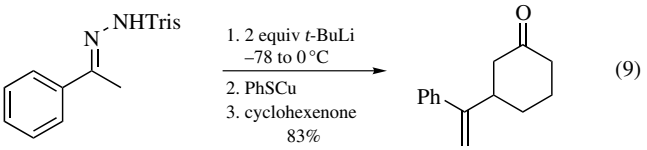


(7)



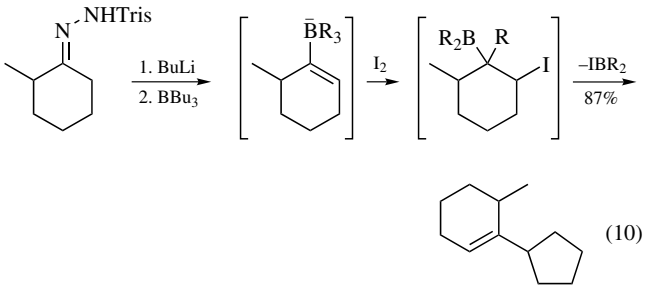
(8)

Several investigators have attenuated the potent nucleophilicity of vinyllithium intermediates by transmetalation or trapping. Vinylstannanes,[17] chromium–carbene complexes,[18] and particularly vinylsilanes[19,20] have been prepared. Alkenyllithiums react faithfully to give 1,2-addition products with α,β-unsaturated ketones, and mixed cuprate reagents have also been prepared with some success by trapping vinyllithiums with phenylthiocopper for 1,4-addition (eq 9).[21,22]



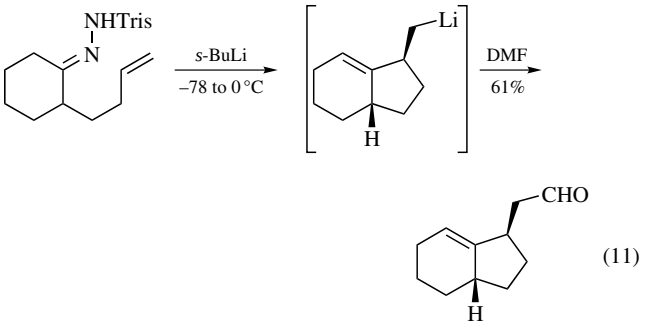
(9)

Intercepting the vinyllithium with a trialkylboron Lewis acid (eq 10) forms an ate complex that can then undergo iodine-promoted alkyl migration and elimination to give excellent yields of hindered trisubstituted alkenes.[23,24] This transformation constitutes a formal S_N2 displacement of a secondary halide and appears generally applicable to cyclic and acyclic ketones.

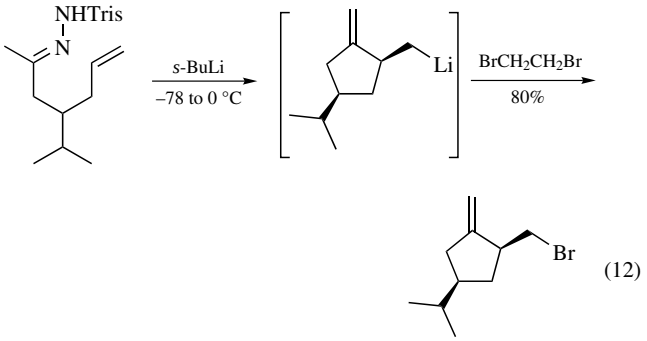


(10)

Intramolecular vinyllithium trapping has been used as an alternative to radical cyclization. Five- to seven-membered ring alkylidene cycloalkanes are formed via S_N2 displacement of a hydrocarbon-tethered leaving group by an alkenyllithium intermediate in 30–72% yield.[25] Another more general alternative is an analogous alkenyllithium condensation with a tether containing an unactivated terminal alkene (eqs 11 and 12).[26,27]



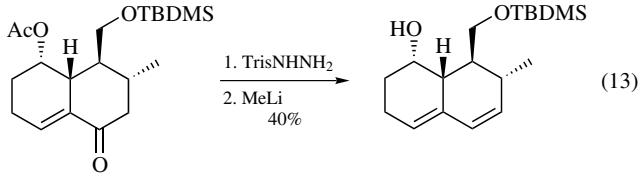
(11)



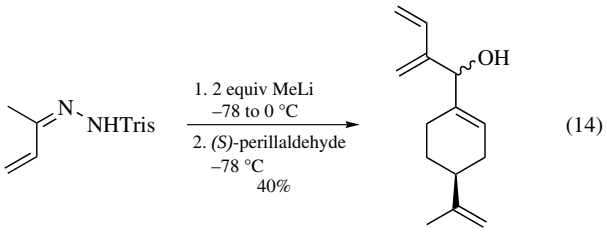
(12)

The resulting alkyllithium produced after cyclization has also been successfully trapped with several electrophiles in fair to excellent yield. This annulation stereoselectively gives the *syn* isomer in 10:1 to >50:1 but is limited to five-membered ring formation and has not been applied to highly functionalized carbocycles.

Condensation of trisylhydrazones with α,β-unsaturated ketones yields hydrazones that are selectively deprotonated α rather than γ to form 2-lithioalkadienes or quenched to form dienes (eqs 13 and 14).[28] 2-Halo ketone hydrazones give the same intermediate after treatment with strong base.[29]



(13)



(14)

Miscellaneous. Ketones may be homologated by one carbon in moderate yield by forming the trisylhydrazone and reacting it with cyanide ion in boiling methanol.[30] 1,2-Carbonyl transpositions are possible in good to excellent yield by sulfenyl- ation of a trisylhydrazone dianion, Shapiro elimination, and hydrolysis of the thioenol ether.[31] Vinylsilanes have been used to the same end.[32] Hydrazones of amides (amidrazones) have been prepared indirectly by treatment of a trisyl carbazate with phosphorus(V) chloride and then morpholine. These compounds act as acyl anion equivalents and may also undergo the Shapiro elimination to form a lithio enamine which can be attacked by two electrophiles.[33] Finally, trisylhydrazones of α-keto amides may be indirectly synthesized from isocyanides; when treated with alkyllithium base, they undergo the Shapiro reaction to give allenylates. These intermediates react with electrophiles to give α-substituted-α,β-unsaturated amides in good to excellent yield.[34]

First Update

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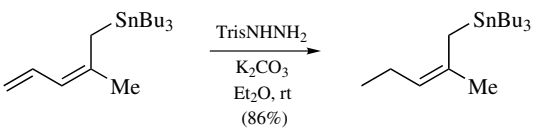
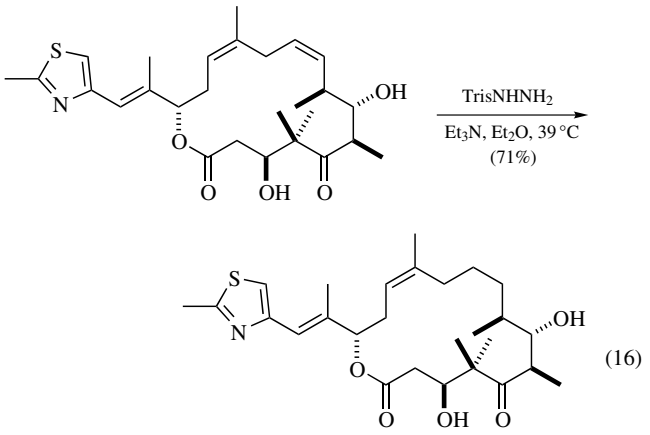
Institute for Research in Biomedicine, Barcelona, Spain

Alkene Reduction. Sulfonylhydrazides decompose into diimide and sulfonic acid when heated. For this reason, they have been utilized in the reduction of unsaturated compounds. When 2,4,6-triisopropylbenzenesulfonylhydrazide (TPSH) is used, the diimide can be generated at room temperature in the presence of base to reduce mono- or disubstituted double bonds selectively in the presence of trisubstituted alkenes (eq 15).[35] This reduction method tolerates sensitive groups such as esters, ketones, or organocobalt complexes[36] and has been applied in the preparation of polymers[37] and in the synthesis of natural products (eq 16).[38] This reagent was not effective in the reduction of resin-bound cyclic peptides.[39]



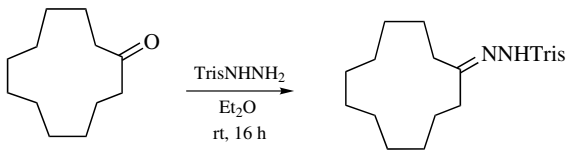
(15)

Tris = 2,4,6-triisopropylbenzenesulfonyl



(16)

Formation of Hydrazones. Most of the chemistry developed with TPSH has been done with the corresponding hydrazones obtained by condensation with ketones and aldehydes. The condensation usually takes place by mixing equimolar quantities of TPSH and the carbonyl compound in a protic solvent such as ethanol or methanol with a catalytic amount of acid at room temperature.[40] Different solvents and acid-free conditions have been employed as well (eq 17).[41] The hydrazones are stable and can be isolated by filtration or flash chromatography.

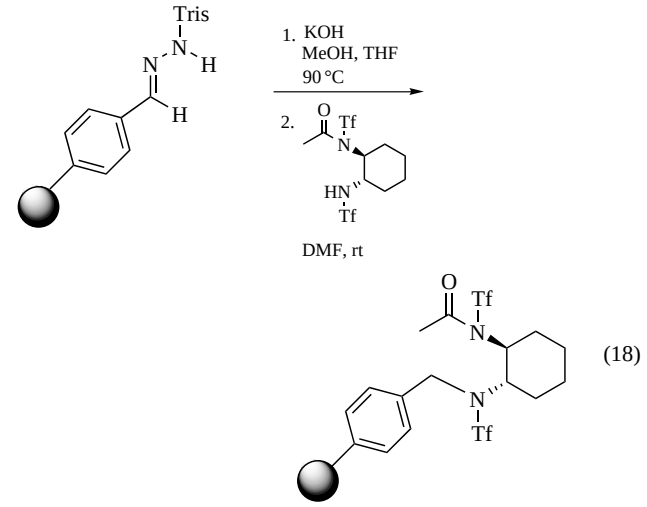


(17)

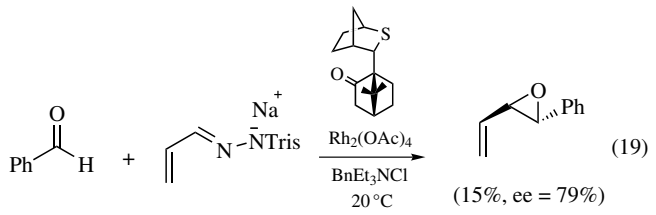
(69%)

Bamford–Stevens and Shapiro Reactions. The Bamford–Stevens reaction is used to obtain unsaturated compounds from tosylhydrazones. A base is required to generate its monoanion, which thermally decomposes to yield the corresponding diazo derivatives. These reactive species evolve to give an alkene through carbenium ions in protic solvents or carbenes in aprotic solvents. The thermal decomposition of the monoanions of trisylhydrazones is commonly used to obtain diazoalkanes for different applications such as functionalization of solid supports,[42] epoxidation and alkenylation of aldehydes,[43] or the study of radicals and carbenes.[44–46] The functionalization of a Merrifield resin with chiral reagents has been achieved by heating a trisylhydrazone derivative in the presence of base. Then, the addition of the chiral sulfonamide ligand to the diazoalkane generated on the Merrifield resin gave rise to the chiral supported reagent (eq 18).[47]

The temperature required for the formation of diazoalkanes can be significantly decreased by using phase-transfer catalysis. This method has allowed the use of transition metals in the catalytic asymmetric epoxidation of carbonyl compounds (eq 19).[48] The use of phase-transfer catalysis and moderate temperatures promotes the formation of diazoalkanes at a very low rate, achieving low concentrations of diazoalkane during the reaction, which is critical for the outcome of the process. The use of trisylhydrazone has shown better results in some cases compared to its tosyl analog. Presumably, the bulkier sulfonyl group may facilitate the decomposition of the salt at lower temperatures, preventing side reactions.

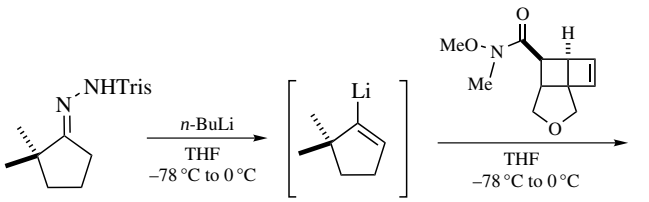


(18)



(19)

The Shapiro reaction is a variation of the Bamford–Stevens reaction, where the addition of an excess of an organolithium reagent (3.5–4.5 equiv) at low temperature is required. Under these conditions, a lithium diazonium salt is formed that decomposes, giving rise to a vinyllithium intermediate, when the reaction is warmed to 0 °C or room temperature. The use of 2,4,6-triisopropylbenzenesulfonylhydrazones instead of its tosyl analogs prevents the *ortho*-metalation, reducing the amount of organolithium reagent required (2 equiv). The vinyllithium obtained may be trapped with a variety of electrophiles such as aldehydes,[49–55] ketones,[56–60] esters,[61] DMF,[62,63] CO_2,[64] H_2O,[65] D_2O,[66] or halides.[67] When the vinyllithium is added to a Weinreb amide, the corresponding enones are obtained (eq 20).[68]

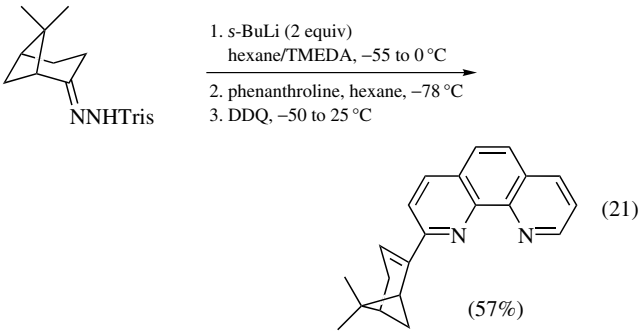


(20)

(82%)

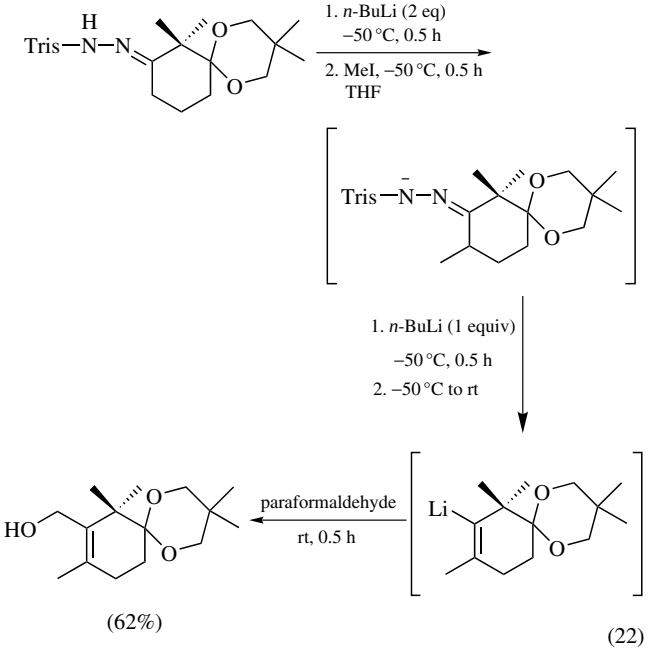
The Shapiro reaction has been utilized in the functionalization of phenanthroline to obtain chiral ligands.[69] The vinyllithium generated with 2 equiv of *s*-BuLi was trapped with phenanthroline,

and after rearomatization with DDQ to recover the phenanthroline system the chiral ligand was obtained (eq 21).



(21)

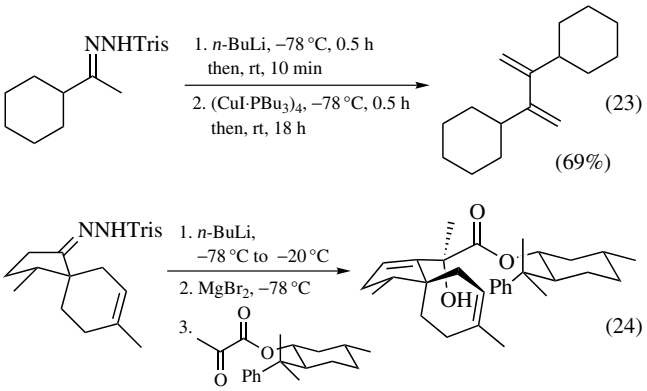
Alpha alkylation of hydrazones and Shapiro reaction in a one-pot process provides a versatile route to tetrasubstituted alkenes. The addition of 2 equiv of butyllithium to a trisylhydrazone generates a dianion, which may be trapped at low temperature with different electrophiles such as methyl iodide. An additional equivalent of butyllithium generates a dianion species that decomposes at room temperature to yield the vinyllithium intermediate of the Shapiro reaction. This type of compound can react with different electrophiles as commented before. In this example, the final addition of paraformaldehyde gave rise to the tetrasubstituted alkene represented in eq 22.[70]



(22)

The vinyllithium intermediate generated through the Shapiro reaction has been utilized to obtain different organometallic compounds such as vinylstannanes,[71–74] which can then react with different electrophiles or undergo cross-coupling reactions.[75]

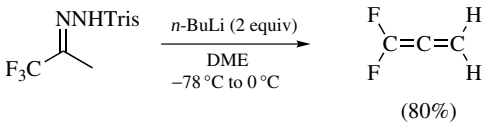
Transmetallation with copper leads to reagents that can react with electrophiles[76]and also evolve through an oxidative dimerization process, giving rise to 1,3-dienes (eq 23).[77] The exchange of lithium for magnesium has been used on diastereoselective additions to ketones (eq 24).[78]



(23)

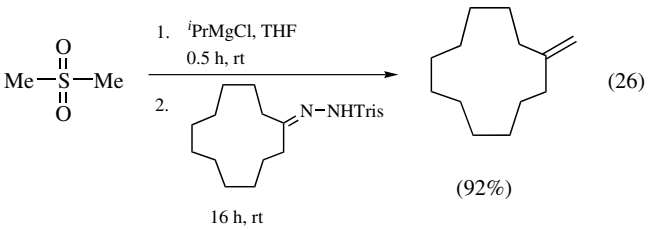
(24)

When the Shapiro reaction is carried out on trifluoromethylhydrazones, the vinyllithium intermediate undergoes defluorination prior to trapping to give 1,1-difluoroallenes (eq 25).[79]



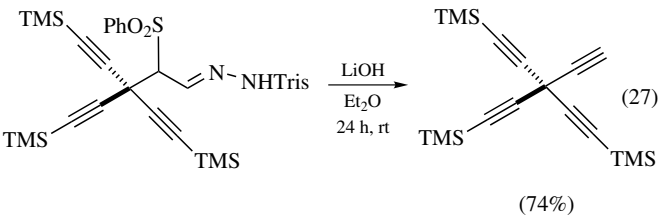
(25)

Alkene Formation. Tosylhydrazones can be transformed into alkenes by the addition of α-magnesioalkyl sulfones at room temperature. The use of magnesium instead of lithium leads to smoother reactions with less fragmentation and prevents the formation of Shapiro products.[80] Trisylhydrazones have shown better results than the corresponding tosylhydrazones and have been utilized in the synthesis of exomethylenecycloalkanes such as exomethylenecyclododecane (eq 26).[41]



(26)

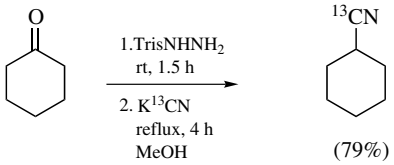
Alkyne Formation. Tetraethynylmethane was obtained from a trisylhydrazone α-sulfonyl-substituted derivative, which in the presence of base gave rise to the final alkynyl moiety of the molecule (eq 27).[81,82] Alkynes may also be obtained from α-bromoketones and trisylhydrazines in acid media after calefaction, but in lower yields.[83]



(27)

Nitrile Formation. Homologation of carbonyl groups to obtain nitriles can be performed in a one-pot procedure, by forming first the corresponding hydrazone followed by the addition of

KCN and calefaction of the mixture. Under these conditions, the cyanide anion is added to the carbonyl group and the high temperature promotes the elimination of the hydrazine moiety. The use of trisylhydrazones instead of the tosyl analogs reduces the temperature required, giving rise to nitrile derivatives in good yields.[84,85] This transformation has been utilized in the isotopic labeling of metabolites (eq 28).

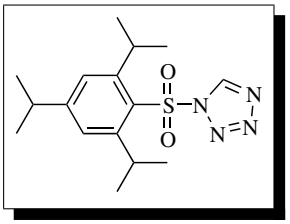


(28)

1. Chamberlin, A. R.; Bloom, S. H., *Org. React.* **1990**, *39*, 1.
2. Lohrmann, R.; Khorana, H. G., *J. Am. Chem. Soc.* **1966**, *88*, 829.
3. Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B., *Tetrahedron* **1976**, *32*, 2157.
4. Cusack, N. J.; Reese, C. B.; Roozpeikar, B., *J. Chem. Soc., Chem. Commun.* **1972**, 1132.
5. Garbisch, E. W., Jr.; Schildcrout, S. M.; Patterson, D. B.; Sprecher, C. M., *J. Am. Chem. Soc.* **1965**, *87*, 2932.
6. For a review of diazene reduction of alkenes, see Hünig, S.; Müller, H. R.; Thier, W., *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271.
7. Bertz, S. H.; Dabbagh, G., *J. Org. Chem.* **1983**, *48*, 116.
8. Smith, A. B., III; Jerris, P. J., *J. Org. Chem.* **1982**, *47*, 1845.
9. (a) Adlington, R. M.; Barrett, A. G. M., *J. Chem. Soc., Perkin Trans. 1* **1981**, 2848. (b) Adlington, R. M.; Barrett, A. G. M., *J. Chem. Soc., Chem. Commun.* **1979**, 1122. (c) Adlington, R. M.; Barrett, A. G. M., *J. Chem. Soc., Chem. Commun.* **1978**, 1071. (d) Bond, F. T.; DiPietro, R. A., *J. Org. Chem.* **1981**, *46*, 1315. (e) Engel, P. S.; Culotta, A. M., *J. Am. Chem. Soc.* **1991**, *113*, 2686.
10. Bergbreiter, D. E.; Newcomb, M. *Asymmetric Synthesis*; Academic: San Diego, 1983; Vol. 2.
11. Chamberlin, A. R.; Bond, F. T., *Synthesis* **1979**, 44.
12. (a) Chamberlin, A. R.; Bond, F. T., *J. Org. Chem.* **1978**, *43*, 147. (b) Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L.; Capuan, L. A., *Tetrahedron Lett.* **1975**, 1811. (c) Traas, P. C.; Boelens, H.; Tokken, H. J., *Tetrahedron Lett.* **1976**, 2287. (d) Jones, F. K.; Denmark, S. E., *Helv. Chim. Acta.* **1983**, *66*, 2377.
13. Shapiro, R. H., *Org. React.* **1976**, *23*, 405.
14. (a) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T., *J. Org. Chem.* **1978**, *43*, 154. (b) Dudman, C. C.; Grice, P.; Reese, C. B., *Tetrahedron Lett.* **1980**, *21*, 4645. (c) Dudman, C. C.; Reese, C. B., *Synthesis* **1982**, 419. (d) Ok, H.; Caldwell, C.; Schroeder, D. R.; Singh, A. K.; Nakanishi, K., *Tetrahedron Lett.* **1988**, *29*, 2275. (e) Jin, F.; Xu, Y.; Ma, Y., *Tetrahedron Lett.* **1992**, *33*, 6161. (f) Dirdonan, C. D.; Reese, C. B., *Synthesis* **1982**, 419.
15. (a) Chamberlin, A. R.; Liotta, E. L.; Bond, F. T., *Org. Synth.* **1983**, *61*, 141. (b) Engel, P. S.; Culotta, A. M., *J. Am. Chem. Soc.* **1991**, *113*, 2686. (c) Schore, N. E.; Knudsen, M. J., *J. Org. Chem.* **1987**, *52*, 569.
16. (a) Oppolzer, W.; Begley, T.; Ashcroft, A., *Tetrahedron Lett.* **1984**, *25*, 825. (b) Wasserman, H. H.; Fukuyama, J. M., *Tetrahedron Lett.* **1984**, *25*, 1387. (c) Mislanker, D. G.; Mugrage, B.; Darling, S. D., *Tetrahedron Lett.* **1981**, *22*, 4619. (d) Baudouy, R.; Sartoretti, J., *Tetrahedron* **1983**, *39*, 3293.
17. Corey, E. J.; Estreicher, H., *Tetrahedron Lett.* **1980**, *21*, 1113.
18. Wulff, W. D.; Tang, P.-C.; Chan, K.-S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R., *Tetrahedron* **1985**, *41*, 5813.
19. Daniels, R. G.; Paquette, L. A., *Organometallics* **1982**, *1*, 1449.
20. Stevens, K. E.; Paquette, L. A., *Tetrahedron Lett.* **1981**, *22*, 4393.
21. Stemke, J. R.; Chamberlin, A. R.; Bond, F. T., *Tetrahedron Lett.* **1976**, 2947.
22. Kende, A. S.; Jungheim, L. N., *Tetrahedron Lett.* **1980**, *21*, 3849.
23. Baba, T.; Avasthi, K.; Suzuki, A., *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1571.
24. Avasthi, K.; Baba, T.; Suzuki, A., *Tetrahedron Lett.* **1980**, *21*, 945.
25. Chamberlin, A. R.; Bloom, S. H., *Tetrahedron Lett.* **1984**, *25*, 4901.
26. Chamberlin, A. R.; Bloom, S. H., *Tetrahedron Lett.* **1986**, *27*, 551.
27. Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H., *J. Am. Chem. Soc.* **1988**, *110*, 4788.
28. (a) Kozikowski, A. P.; Li, C.-H., *J. Org. Chem.* **1987**, *52*, 3541. (b) Brown, P. A.; Jenkins, P. R., *J. Chem. Soc., Perkin Trans. 1* **1986**, 1129. (c) Brown, P. A.; Jenkins, P. R., *Tetrahedron Lett.* **1982**, *23*, 3733.
29. Paquette, L. A.; Daniels, R. G.; Gleiter, R., *Organometallics* **1984**, *3*, 560.
30. Jiricny, J.; Orere, D. M.; Reese, C. B., *J. Chem. Soc., Perkin Trans. 1* **1980**, 1487.
31. Mimura, T.; Nakai, T., *Chem. Lett.* **1980**, 931.
32. Fristad, W. E.; Bailey, T. B.; Paquette, L. A., *J. Org. Chem.* **1978**, *43*, 1620.
33. Baldwin, J. E.; Bottaro, J. C., *J. Chem. Soc., Chem. Commun.* **1981**, 1121.
34. (a) Adlington, R. M.; Barrett, A. G. M.; Quayle, P.; Walker, A., *J. Chem. Soc., Perkin Trans. 1* **1983**, 605. (b) Adlington, R. M.; Barrett, A. G. M., *J. Chem. Soc., Chem. Commun.* **1981**, 65. (c) Adlington, R. M.; Barrett, A. G. M., *Tetrahedron* **1981**, *37*, 3935.
35. Nishigaichi, Y.; Ishida, N.; Takuwa, A., *Bull. Chem. Soc. Jpn.* **1994**, *67*, 274.
36. Liu, T.-Z.; Li, J.-M.; Isobe, M., *Tetrahedron* **2000**, *56*, 10209.
37. Mahittikul, A.; Prasassarakich, P.; Rempel, G. L., *J. Appl. Polym. Sci.* **2007**, *103*, 2885.
38. Ermolenko, M. S.; Potier, P., *Tetrahedron Lett.* **2002**, *43*, 2895.
39. Pattabiraman, V. R.; Stymiest, J. L.; Derksen, D. J.; Martin, N. I.; Vederas, J. C., *Org. Lett.* **2007**, *9*, 699.
40. Bourgeois, D.; Prunet, J.; Pancrazi, A.; Prangé, T.; Lallemand, J.-Y., *Eur. J. Org. Chem.* **2000**, 4029.
41. Kurek-Tyrlik, A.; Marczak, S.; Michalak, K.; Wicha, J.; Zarecki, A., *J. Org. Chem.* **2001**, *66*, 6994.
42. Bhalay, G.; Dunstan, A. R., *Tetrahedron Lett.* **1998**, *39*, 7803.
43. Zhu, S.; Xing, C.; Pang, W.; Zhu, S., *Tetrahedron Lett.* **2006**, *47*, 5897.
44. Creary, X.; Mehrsheikh-Mohammadi, M. E.; McDonald, S., *J. Org. Chem.* **1989**, *54*, 2904.
45. Nicolaides, A.; Matsushita, T.; Yonezawa, K.; Sawai, S.; Tomioka, H.; Stracener, L. L.; Hodges, J. A.; MacMahon, R. J., *J. Am. Chem. Soc.* **2001**, *123*, 2870.
46. DePinto, J. T.; deProphetis, W. A.; Menke, J. L.; McMahon, R. J., *J. Am. Chem. Soc.* **2007**, *129*, 2308.
47. Arseniyadis, S.; Subhash, P. V.; Valleix, A.; Wagner, A.; Mioskowski, C., *Chem. Commun.* **2005**, *26*, 3310.
48. Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L., *J. Am. Chem. Soc.* **2003**, *125*, 10926.
49. Denmark, S. E.; Habermas, K. L.; Hite, G. A., *Helv. Chim. Acta* **1988**, *71*, 168.
50. Cheng, K.-F.; Chan, K.-P.; Kong, Y.-C.; Ho, D.-D., *J. Chem. Soc., Perkin Trans. 1* **1991**, *12*, 2955.
51. Cheng, K.-F.; Chan, K.-P.; Lai, T.-F., *J. Chem. Soc., Perkin Trans. 1* **1991**, 2461.
52. Engel, P. S.; Culotta, A. M., *J. Am. Chem. Soc.* **1991**, *113*, 2686.
53. Seck, M.; Seon-Meniel, B.; Jullian, J.-C.; Franck, X.; Hocquemiller, R.; Figadère, B., *Lett. Org. Chem.* **2006**, *3*, 309.
54. Hu, X.-D.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.-A.; Wang, M., *Org. Lett.* **2006**, *8*, 1823.

55. Bourgeois, D.; Lallemand, J.-Y.; Pancrazi, A.; Prunet, J., *Synlett* **1999**, *10*, 1555.
56. Rupert, K. C.; Liu, C. C.; Nguyen, T. T.; Whitener, M. A.; Sowa, J. R., Jr., *Organometallics* **2002**, *21*, 144.
57. Liu, C.; Sowa, J. R., Jr., *Tetrahedron Lett.* **1996**, *37*, 7241.
58. Alder, R. W.; Colclough, D.; Grams, F.; Orpen, A. G., *Tetrahedron* **1990**, *46*, 7933.
59. Erker, G.; Wilker, S., *Organometallics* **1993**, *12*, 2140.
60. Tamiya, J.; Sorensen, E. J., *Tetrahedron* **2003**, *59*, 6921.
61. Erker, G.; Schamberger, J.; Van der Zeijden, A. A. H.; Dehnicke, S.; Krüger, C.; Goddard, R.; Nolte, M., *J. Organomet. Chem.* **1993**, *459*, 107.
62. Shanmugham, M. S.; White, J. D., *Chem. Commun.* **2004**, *1*, 44.
63. Roy, O.; Pattenden, G.; Pryde, D. C.; Wilson, C., *Tetrahedron* **2003**, *59*, 5115.
64. Nikas, S. P.; Thakur, G. A.; Parrish, D.; Alapafuja, S. O.; Huestis, M. A.; Makriyannis, A., *Tetrahedron* **2007**, *63*, 8112.
65. Chrobok, A.; Gössinger, E.; Orglmeister, E.; Pflugseder, K.; Schwaiger, J.; Wuggenig, F., *Tetrahedron* **2007**, *63*, 8311.
66. Nelsen, S. F.; Reinhardt, L. A.; Tran, H. Q.; Clark, T.; Chen, G.-F.; Pappas, R. S.; Williams, F., *Chem. Eur. J.* **2002**, *8*, 1074.
67. Brandt, K.; Haas, A.; Hardt, T.; Mayer-Figge, H.; Merz, K.; Wallmichrath, T., *J. Fluorine Chem.* **1999**, *97*, 115.
68. Bader, S. J.; Snapper, M. L., *J. Am. Chem. Soc.* **2005**, *127*, 1201.
69. Peña-Cabrera, E.; Norrby, P.-O.; Sjögren, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Åkermark, B.; Helquist, P., *J. Am. Chem. Soc.* **1996**, *118*, 4299.
70. Tormakangas, O. P.; Toivola, R. J.; Karvinen, E. K.; Koskien, A. M. P., *Tetrahedron* **2002**, *58*, 2175.
71. Nordvall, G.; Sundquist, S.; Nilvebrant, L.; Hacksell, U., *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2837.
72. Barrett, A. G. M.; Boys, M. L.; Boehm, T. L., *J. Org. Chem.* **1996**, *61*, 685.
73. Matsuura, A.; Komatsu, K., *J. Am. Chem. Soc.* **2001**, *123*, 1768.
74. Bennasar, M.-L.; Juan, C.; Roca, T.; Monerris, M.; Bosch, J., *Tetrahedron* **2001**, *57*, 10125.
75. Mazzola, R. D, Jr.; Giese, S.; Benson, C. L.; West, F. G., *J. Org. Chem.* **2004**, *69*, 220.
76. Révész, L.; Hiestand, P.; La Vecchia, L.; Naef, R.; Naegeli, H.-U.; Oberer, L.; Roth, H.-J., *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1521.
77. Addie, M. S.; Taylor, R. J. K., *ARKIVOC (Gainesville, FL, U. S.)* **2000**, *1*, 660.
78. Tamiya, J.; Sorensen, E. J., *J. Am. Chem. Soc.* **2000**, *122*, 9556.
79. Shi, G.; Xu, Y., *J. Fluorine Chem.* **1989**, *44*, 161.
80. Vedejs, E.; Dolphin, J. M.; Stolle, W. T., *J. Am. Chem. Soc.* **1979**, *101*, 249.
81. Feldman, K. S.; Kraebel, C. M.; Parvez, M., *J. Am. Chem. Soc.* **1993**, *115*, 3846.
82. Feldman, K. S.; Weinreb, C. K.; Youngs, W. J.; Bradshaw, J. D., *J. Am. Chem. Soc.* **1994**, *116*, 9019.
83. Bryant, M. W.; Smith, R. A. J.; Wong, L., *Aust. J. Chem.* **1982**, *35*, 2529.
84. Bellemin, R.; Decerprit, J.; Festal, D., *Eur. J. Med. Chem.* **1996**, *31*, 123.
85. Sekiyama, Y.; Palaniappan, N.; Reynolds, K. A.; Osada, H., *Tetrahedron* **2003**, *59*, 7465.

Triisopropylbenzenesulfonyl Tetrazole



[59126-88-0] $C_{16}H_{24}N_4O_2S$ (MW 336.16)

InChI = 1/C16H24N4O2S/c1-10(2)13-7-14(11(3)4)16(15(8-13)12(5)6)23(21,22)20-9-17-18-19-20/h7-12H,1-6H3

InChIKey = PWLNMVIUTUFFSG-UHFFFAOYAS

(useful as a condensing or coupling reagent for phosphoester formation in oligonucleotide synthesis)

Alternate Name: 1-(2,4,6-triisopropylbenzenesulfonyl)tetrazole; TPS-tetrazole.

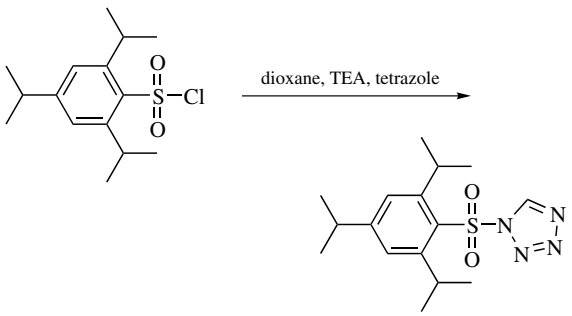
Physical Data: white crystals; mp 95–97 °C (crystallized from benzene/ petroleum ether). NMR ($CDCl_3$): δ 9.28 (s, 1H, CH in tetrazole), 7.40 (s, 2H, aromatic), 4.15 (m, 2H, CH ortho to isopropyl), 3.14 (m, 1H, CH para to isopropyl), 1.28 (m, 18H, CH_3).[1]

Solubility: soluble in pyridine, chloroform, and dioxane.

Form Supplied in: prepare immediately before use by the reaction of 2,4,6-triisopropylbenzenesulfonyl chloride with tetrazole.

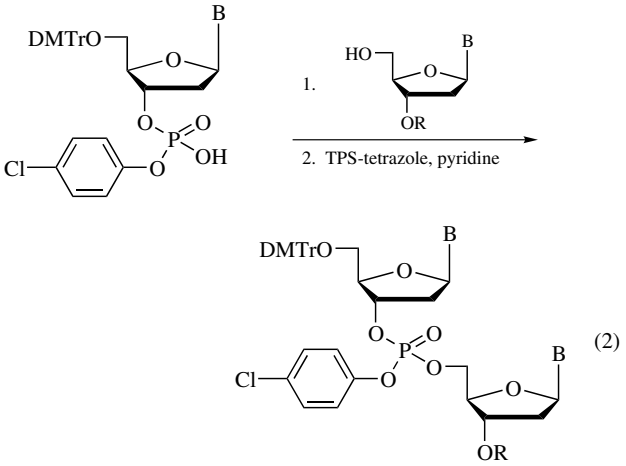
Handling, Storage, and Precaution: all arylsulfonyl tetrazoles decompose on storage in a desiccator, and the most unstable is benzenesulfonyltetrazole which decomposes completely in 10 days. It is advisable to prepare triisopropylbenzenesulfonyl tetrazole freshly before use.

Preparation of 1-(2,4,6-Triisopropylbenzenesulfonyl) Tetrazole.[1–3] To a solution of dioxane (2 ml) containing triethylamine (10.1 mmol) is added, with cooling, triisopropylbenzenesulfonyl chloride (10 mmol) and tetrazole (10 mmol) (eq 1). After 2 h, the precipitate is filtered off, discarded, and the filtrate is evaporated to dryness. The solid residue is dissolved in chloroform (50 ml) and washed with water (2×20 ml). The chloroform solution is dried (anhydrous Na_2SO_4) and, after evaporation of the solvent, the residue is crystallized from benzene/ petroleum ether.



(1)

Syntheses of Di-, Tri-, and Oligo-deoxynucleotides of Natural Origin.[4–8] An important consideration in the chemical synthesis of oligodeoxynucleotides by the phosphotriester method is the choice of the coupling reagent for the reaction between the 3′-phosphodiester of one deoxynucleotide unit and the 5′-hydroxyl group of the protected deoxynucleoside of the second unit to produce the dinucleoside-3′,5′-phosphotriester. For example, arylsulfonyl triazoles have been reported as useful condensing reagents for oligonucleotide synthesis, and this triester method is capable of producing large amounts of biologically active deoxyoligonucleotides with defined base sequences. However, despite their effectiveness, especially in the synthesis of deoxyoligonucleotides with guanosine containing units, condensations with arylsulfonyl triazoles are sluggish in terms of completion of the condensation reactions. Efforts to improve the triester methodology led to the development of arylsulfonyl tetrazole as a more effective coupling reagent. An example of the synthesis of a dinucleotide is illustrated in eq 2.

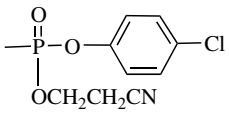


(2)

DMTr = 4,4′-dimethoxytrityl

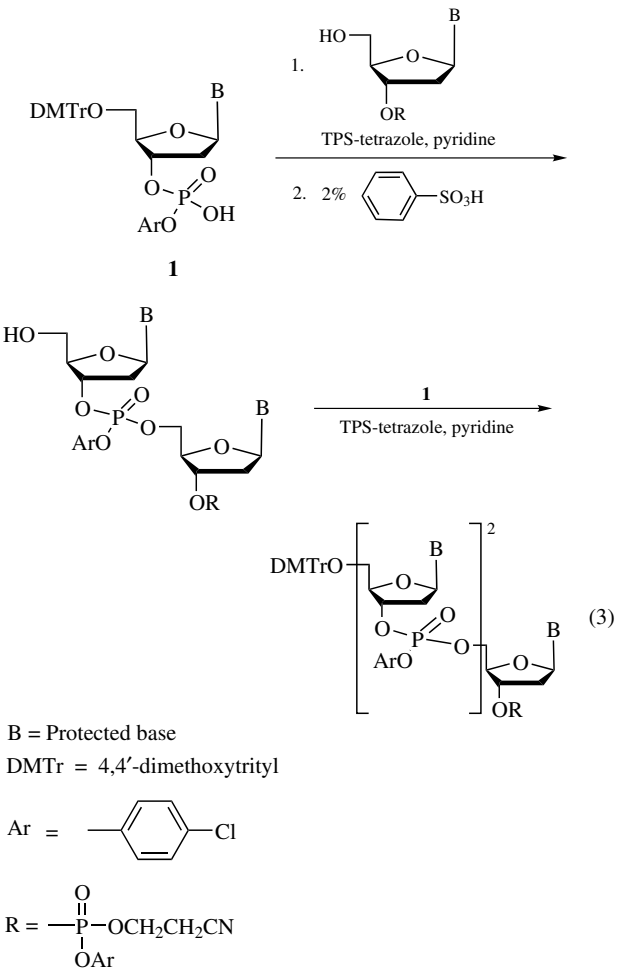
B = *N*-protected base, thymine

R = Bz, Ac, 4-methoxybenzoyl,



Synthesis of a trinucleotide is illustrated below, in eq 3, as an example of a small DNA preparation.

Solid-phase Synthesis of Oligonucleotides.[9–13] The solid-phase synthetic approach for preparing polynucleotides of defined sequences is potentially very useful, and this methodology is precedented by the successful synthesis of polypeptides on various polymer supports (e.g., polyacrylamide resins). Several essential features are necessary for the block-coupling phosphotriester methodology on a polymer support. These features and the coupling steps are as follows: (i) the sequential addition, in the presence of a coupling reagent (e.g., 2,4,6-triisopropylbenzenesulfonyl tetrazole), of an appropriate trinucleotide or other small oligonucleotide blocks to the polyacrylamide or other solid-support containing the 3′-bound and 5′-free hydroxyl groups of a deoxynucleoside; (ii) protection of any unreacted 5′-hydroxyl group of the deoxynucleoside with acetic anhydride; (iii) deprotection of the dimethoxytrityl group from the oligonucleotide, bound to the polymer resin, to afford terminal 5′-hydroxyl groups for the next coupling step (eq 4).



B = Protected base

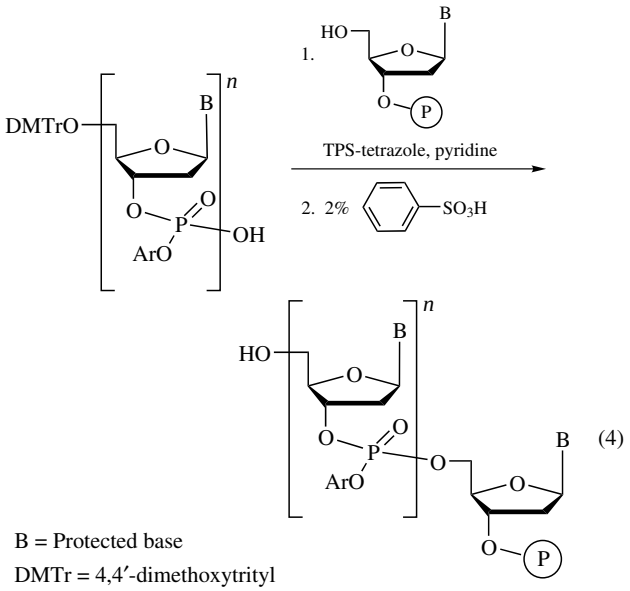
DMTr = 4,4′-dimethoxytrityl

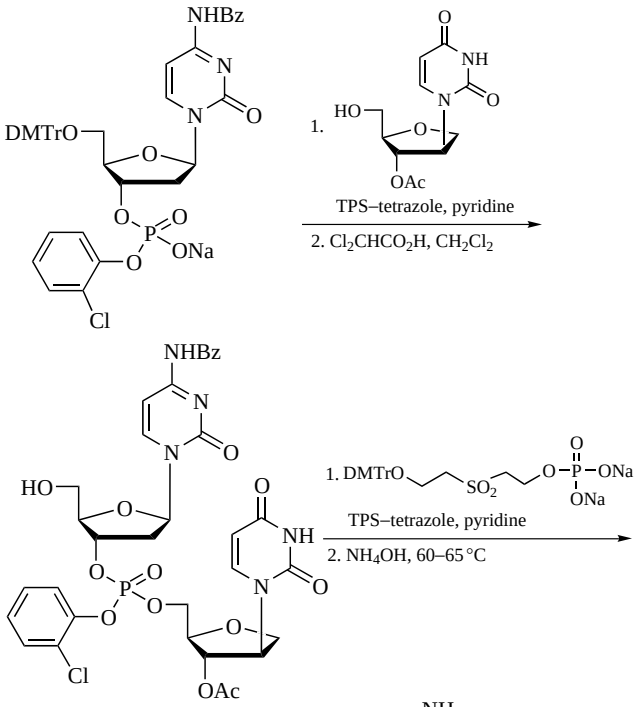
Ar =

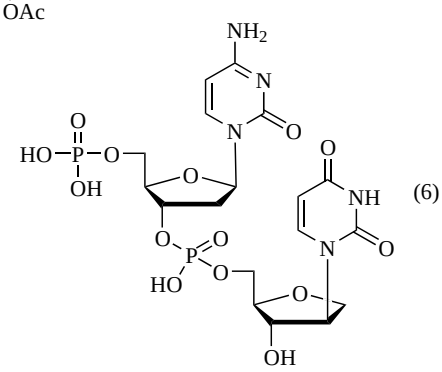
R =

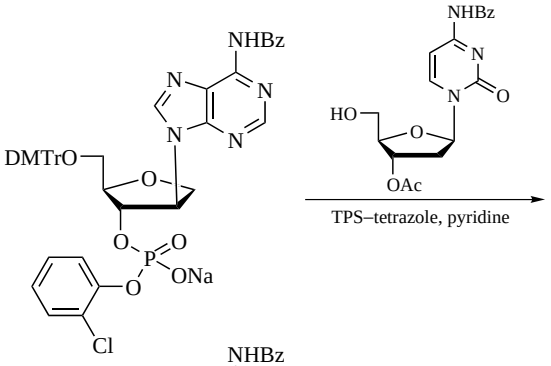
Synthesis of Non-natural Dinucleotides.[14–16] Internucleotide coupling of non-natural nucleoside derivatives can also be carried out with 2,4,6-triisopropylbenzenesulfonyl tetrazole. For example, in our search for clinically useful anti-HIV integrase agents, we designed and synthesized non-natural dinucleotides with nuclease-resistant internucleotide phosphodiester bonds and with defined base sequences that would be recognized by HIV integrase. These dinucleotides were strong inhibitors of the integrase. A key step in the synthesis of these compounds was the internucleotide coupling reaction. For example, the coupling of the protected (*S*,*S*)-isodeoxyadenosine phosphate ester and 3′-protected deoxycytidine was carried out with 2,4,6-triisopropylbenzenesulfonyl tetrazolide. Subsequent removal of the trityl protecting group and phosphorylation at the 5′-position with 2-cyanoethylphosphate in the presence of DCC, followed by deprotection with NH_4OH gave the HIV integrase inhibitor pisodApdC, as shown below in eq 5.

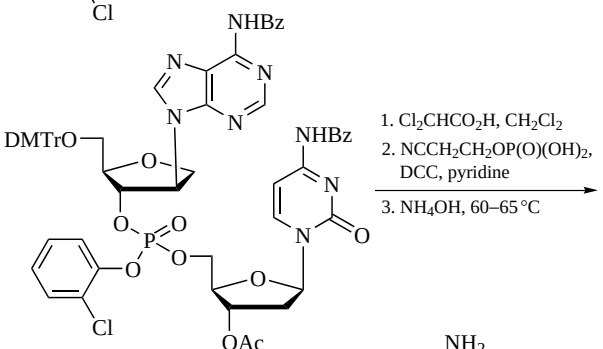
Another example, which involves only pyrimidine bases, illustrates the generality of this coupling reaction (eq 6).

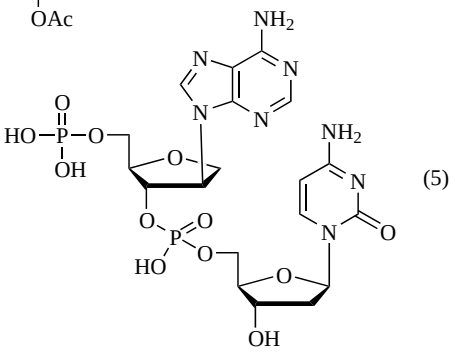












1. Stawinski, J.; Hozumi, T.; Narang, S. A., *Can. J. Chem.* **1976**, *54*, 670.
2. Stawinski, J.; Hozumi, T.; Narang, S. A.; Bahl, C. P.; Wu, R., *Nucleic Acids Research* **1977**, *4*, 353.
3. U. S. Pat. 4059592 (to Narang, S. A.; Stawinski, J.) (1977).
4. Gait, M. J.; Popov, S. G., *Tetrahedron Lett.* **1980**, *21*, 2841.
5. European Pat. EP0001931 (to Itakura, K.) (1979).
6. Kraszewski, A.; Stawinski, J.; Wiewiorowski, M., *Nucleic Acids Research* **1980**, *8*, 2301.
7. Seth, A. K.; Jay, E., *Nucleic Acids Research* **1980**, *8*, 5445.
8. Hirose, T.; Crea, R.; Itakura, K., *Tetrahedron Lett.* **1978**, *28*, 2449.
9. Crea, R.; Hirose, T.; Itakura, K., *Tetrahedron Lett.* **1979**, *20*, 395.
10. Miyoshi, K.-I.; Miyake, T.; Hozumi, T.; Itakura, K., *Nucleic Acids Research* **1980**, *8*, 5473.
11. Dembek, P.; Miyoshi, K.-I.; Itakura, K., *J. Am. Chem. Soc.* **1981**, *103*, 706.
12. Wallace, R. B.; Johnson, M. J.; Hirose, T.; Miyake, T.; Kawashima, E. H.; Itakura, K., *Nucleic Acids Research* **1981**, *9*, 879.
13. U. S. Pat. 4373071 (to Itakura, K.) (1983).
14. Taktakishvili, M.; Neamati, N.; Pommier, Y.; Nair, V., *Bioorg. Med. Chem. Lett.* **2000**, *10*, 249.
15. Taktakishvili, M.; Neamati, N.; Pommier, Y.; Pal, S.; Nair, V., *J. Am. Chem. Soc.* **2000**, *122*, 5671.

16. Taktakishvili, M.; Neamati, N.; Pommier, Y.; Nair, V., *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1433.

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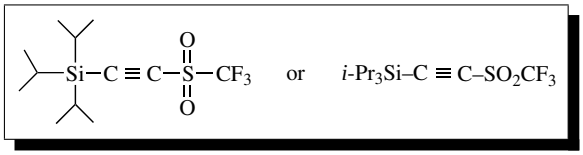
Triisopropylsilylethynyl Triflone



[196789-82-9] $C_{12}H_{21}F_3O_2SSi$ (MW 314.44)
InChI = 1/C12H21F3O2SSi/c1-9(2)19(10(3)4,11(5)6)8-7-18(16,17)12(13,14)15/h9-11H,1-6H3
InChIKey = ROAJHHMTMBSXBG-UHFFFAOYAJ

(reagent for radical alkynylation of C–H or C–I bonds)

Alternate Name: TIPS-acetylene triflone or TIPS-ethynyl triflone.
Solubility: most aprotic organic solvents.
Form Supplied in: colorless liquid not commercially available.
Analysis of Reagent Purity: reagent must be made fresh.
Handling, Storage, and Precaution: sensitive to free radical sources.

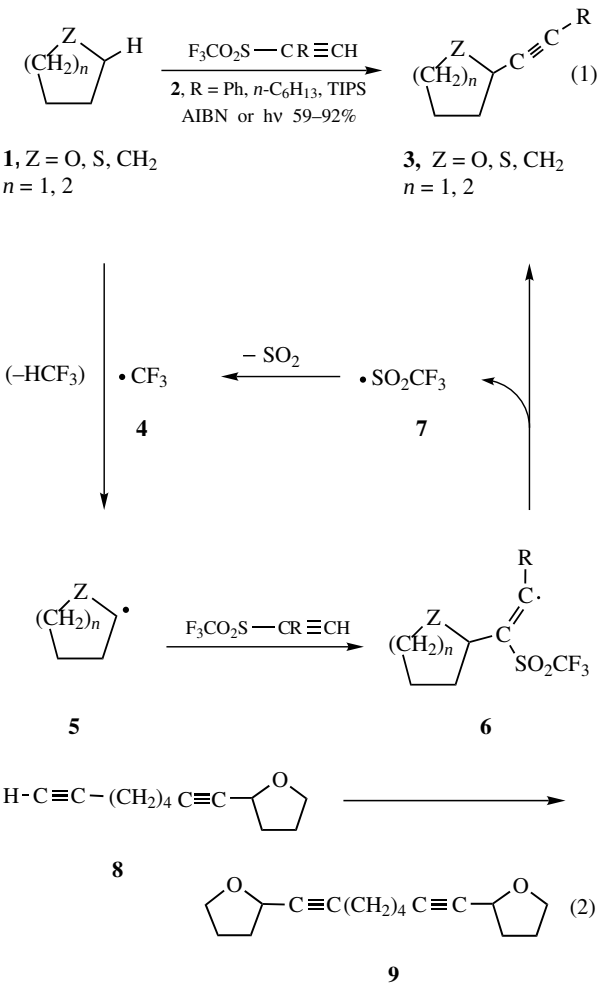
Only two recent papers[1,2] have described this reagent, which is used for free radical initiated alkynylation. In the first paper, the direct alkynylation of C–H bonds proceeds as summarized in eq 1 by the facile C–H bond abstraction by the very electrophilic trifluoromethyl radical **4** generated by cleavage of the CF_3SO_2 radical (**7**) and loss of SO_2. The alkyl radical **5** so generated reacts with the triflone reagent **2** to form the vinyl radical (**6**) which in turn eliminates the SO_2CF_3 radical (**7**) to propagate the chain and afford the attached alkynyl group in **3**.

The TIPS variant in eq 1 is used not only neat on the cyclic C–H substrates THF, tetrahydrothiophene, and cyclohexane, but also in acetonitrile with adamantane, which substituted exclusively at the tertiary C–H (50% yield). Alkynylation was also successful with distal functionality, i.e. R = $(CH_2)_2OSiR_3$ and $(CH_2)_3Cl$, but the triflone could not be formed with ether functionality closer to the acetylene.

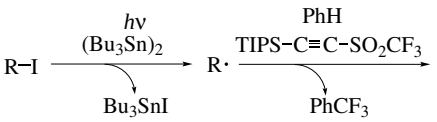
Previously, the alkynylation had been reported[3,4] with other attached hydrocarbon groups (R = Ph and *n*-hexyl in eq 1). The presence of a second acetylene group in the hydrocarbon group R was successful only with four methylenes, but not fewer, separating the two acetylenes. However, with enough separation the outer acetylene succeeded with only H-substitution to yield **8** in eq 2 and the product could be carried through triflation and a second alkynylation to form **9**.

The necessary silyl triflone reagents proved difficult or impossible to make with less hindered silanes (TMS or TBDMS) by the reaction of the silyl-acetylene anion (*n*-BuLi/Et_2O/−78 °C) with Tf_2O. It was this triflation which failed with the proximal ethers and substituted acetylenes above.

In the second paper,[2] the reaction was extended to alkynylate C–I bonds photolytically by the added intermediacy of hexabutyldistannane to generate the radical from the iodide. Bromides were inert in this alkynylation, suggesting that this differential reactivity of the two halogens should prove advantageous in synthetic applications.



The reaction outlined in eq 3, was conducted photolytically in benzene solution, with the benzene presumably scavenging the trifluoromethyl radical, as it is scavenged in eq 2. A dozen examples of iodides were successful in yields generally over 60% and with retention of configuration. These room-temperature examples show the reaction to be compatible with such diverse functionality as free hydroxyl, ester, amide, thiazole, and potential β-elimination substrates, and succeeded with primary, secondary, and tertiary iodides.



The special value of the TIPS group lies in its easy removal (TBAF/25 °C/2 h) to make the acetylene available for further substitution. Furthermore, the present availability of the TIPS-protected acetylene triflone should make possible a further exploration of the addition and cycloaddition reactions of the acetylene activated by the strong electron-withdrawing power of the triflone group.

1. Xiang, J.; Jiang W.; Fuchs, P. L., *Tetrahedron Lett.* **1997**, *38*, 6635.
2. Xiang, J.; Fuchs, P. L., *Tetrahedron Lett.* **1998**, *39*, 8597.
3. Gong, J.; Fuchs, P. L., *J. Am. Chem. Soc.* **1996**, *118*, 4486.
4. Xiang, J.; Fuchs, P. L., *Tetrahedron Lett.* **1996**, *37*, 5269.

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Triisopropylsilyl Trifluoromethanesulfonate[1]

$(i\text{-Pr})_3SiOSO_2CF_3$

[80522-42-5] $C_{10}H_{21}F_3O_3SSi$ (MW 306.46)
InChI = 1/C10H21F3O3SSi/c1-7(2)18(8(3)4,9(5)6)16-17(14,15)10(11,12)13/h7-9H,1-6H3
InChIKey = LHJCZOXMCGQVDQ-UHFFFAOYAK

(highly reactive silylating agent and Lewis acid capable of converting primary and secondary alcohols[1] to the corresponding triisopropylsilyl ethers and converting ketones[1] and lactones[2] into their enol silyl ethers; protection of terminal alkynes;[3] promoting conjugate addition of alkynylzinc compounds to α,β-enones;[4] preparation of (triisopropylsilyl)diazomethane[5])

Alternate Name: TIPS triflate.

Physical Data: colorless oil; bp 83–87 °C/1.7 mmHg; *d* 1.173 g cm^{-3}.

Solubility: sol most organic solvents, such as pentane, CH_2Cl_2, etc.

Form Supplied in: liquid; widely available.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 1.6–1.05 (m). although the reagent is commercially available from various vendors, there have been recent observations about *n*-propyldiisopropylsilyl triflate contaminating TIPSOTf. The presence of this impurity is observed easily by proton NMR.[6]

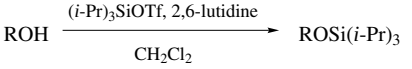
Preparative Methods: to 38.2 g (0.242 mol) of triisopropylsilane at 0 °C under argon is added 23.8 mL (0.266 mol) of trifluoromethanesulfonic acid dropwise. The solution is stirred at 22 °C for 16 h, at which time no further hydrogen gas evolves (removed through a bubbler). The resulting product is distilled through a 30-cm vacuum jacketed Vigreux column under reduced pressure: 71.7 g (97% yield) of TIPS triflate; bp 83–87 °C/1.7 mmHg.[1a]

Handling, Storage, and Precautions: store under argon at 0 °C; unpleasant odor; reacts rapidly with water and other protic solvents.

Original Commentary

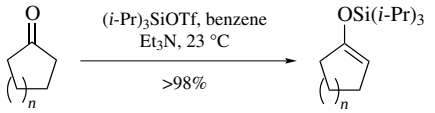
Duy H. Hua & Jinshan Chen
Kansas State University, Manhattan, KS, USA

Silylation of Alcohols.[1] Primary and secondary alcohols are silylated by TIPS triflate in excellent yields. Treatment of 1-phenylethanol with 1.3 equiv of TIPS triflate and 2.5 equiv of 2,6-lutidine in CH_2Cl_2 at 0 °C for 2 h provides a 98% yield of α-(triisopropylsilyloxy)ethylbenzene (eq 1).[1a]



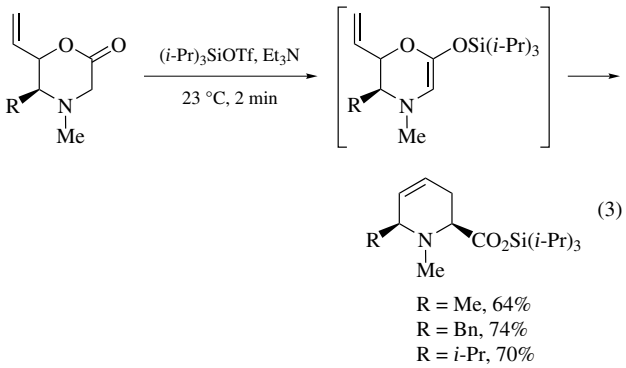
(1)

Formations of Enol Silyl Ethers.[1,2] Aldehydes, ketones, and lactones are readily converted into the corresponding enol TIPS ethers. Reactions of cycloalkanones with 1.1 equiv of TIPS triflate and 1.5 equiv of triethylamine in benzene at 23 °C for 1 h gives >98% yields of the corresponding enol silyl ethers (eq 2).[1a]



(2)

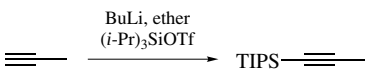
Silylation of 2-morpholinones with 1.2 equiv of TIPS triflate and 1.5 equiv of triethylamine in $CDCl_3$ for 2 min provides silyl ketene acetals, which upon standing at rt undergo Claisen rearrangement to afford pipecolic esters (eq 3).[2]



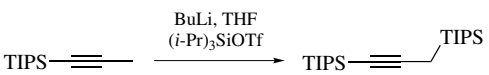
(3)

R = Me, 64%
R = Bn, 74%
R = *i*-Pr, 70%

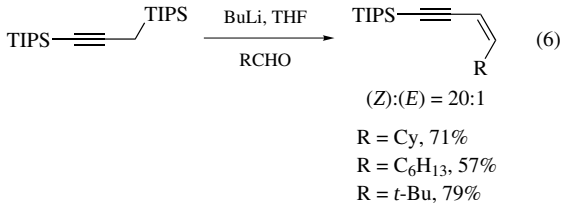
Alkynyltriisopropylsilanes.[3] The acidic alkynic H can be protected with TIPS triflate. Silylation of 1-lithiopropyne with 1 equiv of TIPS triflate in ether at −40 to 0 °C gives an 87% yield of 1-TIPS-propyne (eq 4).[3a] 1,3-Bis(triisopropylsilyl)propyne, derived from treatment of 1-TIPS-propyne with butyllithium in THF at −20 °C for 15 min followed by TIPS triflate at −78 to −40 °C (eq 5), is lithiated with *n*-BuLi in THF at −20 °C for 15 min and then allowed to react with aldehydes (eq 6). The *cis*-enynes are isolated in high yields.[3a] TIPS-propargylmagnesium bromide together with copper(I) iodide has been used in the displacement of the mesylate derivative of farnesol.[3b]



(4)

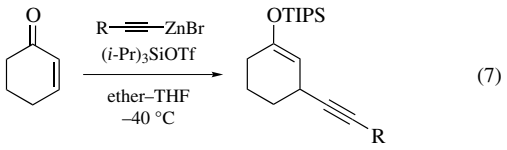


(5)



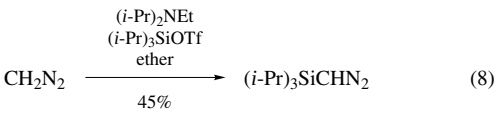
(6)

Conjugate Addition of Alkynylzinc Bromides.[4] Alkynylzinc bromides undergo conjugate addition with α,β-unsaturated ketones in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate or TIPS triflate (trimethylsilyl trifluoromethanesulfonate is also effective) in ether–THF at −40 °C to give the corresponding 1,4-adducts (54–96% yields). A representative example is illustrated in eq 7.



(7)

(Triisopropylsilyl)diazomethane.[5] Silylation of diazomethane with TIPS triflate and diisopropylethylamine in ether at −20 °C to 25 °C gives a 45% yield of (triisopropylsilyl)diazomethane (eq 8).[5] This silylated diazomethane is used to prepare stable silyl-substituted nitrilimines.[5]



(8)

First Update

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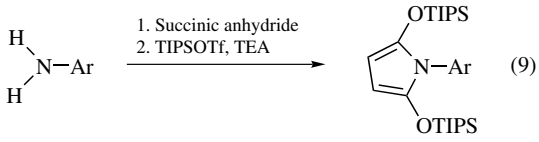
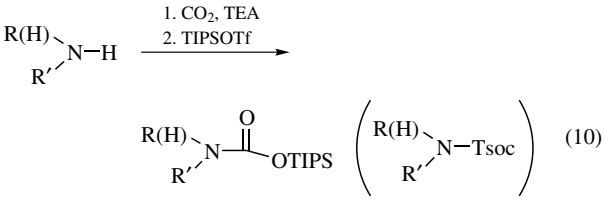
Some highlights on the utility of TIPSOTf published since 1995 are shown below.[7]

Triisopropylsiloxycarbonyl (Tsoc) and BIPSOP Protecting Groups for Amines.[8,9] Two new useful nitrogen protecting groups that rely on the stability of the TIPS group have been developed. In both cases, TIPSOTf was relied on for the formation of the actual amine protecting group. BIPSOP (*N*-substituted-2,5-bis[(triisopropylsilyl)oxy]pyrroles) were formed by reaction of primary amines with succinic anhydride followed by conversion to the bis-siloxypyrrole with TIPSOTf (eq 9). BIPSOP was most useful for the protection of amines under strongly basic reactions. Removal of this protecting group was achieved by treatment with dilute acid followed by hydrazine treatment.



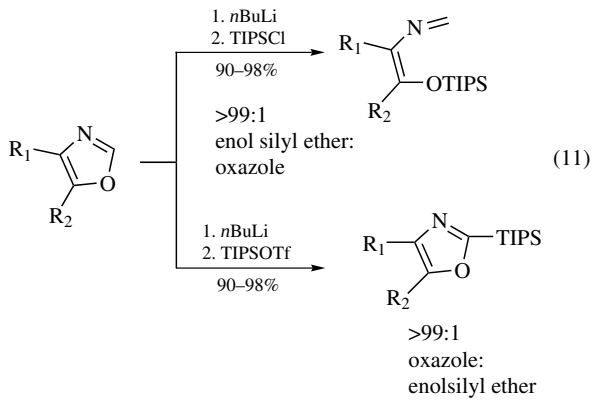
(9)

The Tsoc group was developed for both primary and secondary amine protection and shown to be stable to acid, base, and hydrogenation conditions (eq 10). Removal was achieved with fluoride treatment.

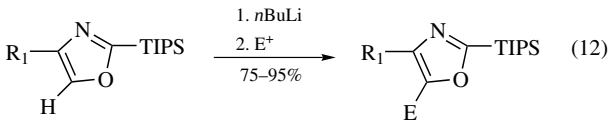


(10)

TIPS Protection for Oxazoles/Regioselective Trapping of C-2 Oxazole Anions. Deprotonation of oxazoles occurs selectively at the C-2 position, and reaction with either TIPS triflate or TIPS chloride gave completely opposite C-silylation or O-silylation selectivity (eq 11).[10] The same remarkable trend was observed for the other, less hindered silyl chloride and -triflates; however, the stability of those products did not allow facile isolation and characterization. The C-2 TIPS oxazole derivative was shown to be stable to strongly basic reactions that allowed further oxazole functionalization (eq 12).[11] Removal of the TIPS group was then achieved with dilute acid.



(11)



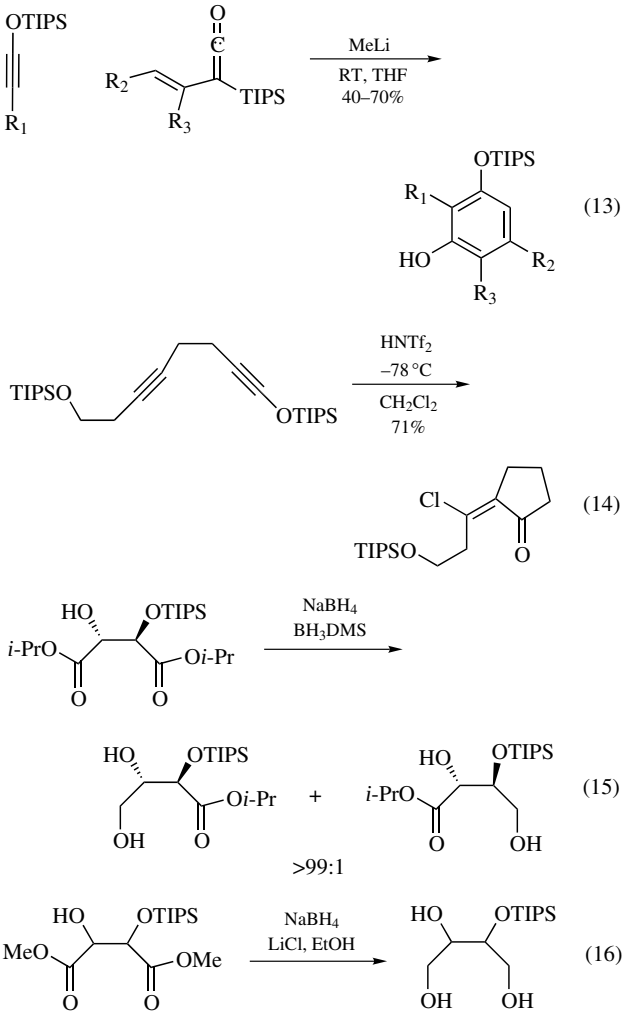
(12)

Benzannulation Using Triisopropylsilyl Vinyl Ketenes. Addition of lithium ynolates generated from ethynylsilyl ethers with silyl vinyl ketenes gave highly substituted benzenes (eq 13).[12] TIPS protection, in contrast to TBDMS, allowed preparation and purification by distillation and silica gel chromatography of these sensitive starting materials.

Cyclization of 1-Silyloxy-1,5-diynes. A $HNTf_2$-promoted 5-*endodig* cyclization of 1-siloxy-1,5-diynes has been shown to give highly selective *B*-halo enones by abstraction of a halogen from halocarbons in good yields (eq 14).[13]

Desymmetrization of Tartaric Acid Esters. Selective reductions of the esters of tartaric acid using TIPS as the controlling element allowed the desymmetrization of tartaric acid and facile access to enantiopure alcohols and diol esters (eqs 15 and

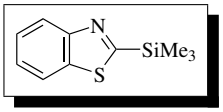
16). Formation of the TIPS protected tartaric acids was achieved in high yields using TIPSOTf as a requirement.[14]



Related Reagents. Triisopropylsilyl Chloride.

1. (a) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H., *Tetrahedron Lett.* **1981**, *22*, 3455. (b) For a review of trialkylsilyltriflates: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G., *Synthesis* **1982**, 1.
2. Angle, S. R.; Breitenbucker, J. G.; Arnaiz, D. O., *J. Org. Chem.* **1992**, *57*, 5947.
3. (a) Corey, E. J.; Rucker, C., *Tetrahedron Lett.* **1982**, *23*, 719. (b) Marshall, J. A.; Andersen, M. W., *J. Org. Chem.* **1992**, *57*, 2766.
4. Kim, S.; Lee, J. M., *Tetrahedron Lett.* **1990**, *31*, 7627.
5. Castan, F.; Baceiredo, A.; Bigg, D.; Bertrand, G., *J. Org. Chem.* **1991**, *56*, 1801.
6. Barden, D. J.; Fleming, I., *J. Chem. Soc., Chem. Commun.* **2001**, 2366.
7. A comprehensive review of all aspects of this reagent (770 references) up to 1995 has been published. See Rucker, C., *Chem. Rev.* **1995**, *95*, 1009.
8. Lipshutz, B. M.; Papa, P.; Keith, J. M., *J. Org. Chem.* **1999**, *64*, 3792.
9. Martin, S. F.; Limberakis, C., *Tetrahedron Lett.* **1997**, *38*, 2617.
10. Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A., *Tetrahedron Lett.* **2002**, *43*, 935.
11. Miller, R. A.; Smith, R. M.; Marcune, B., *J. Org. Chem.* **2005**, *70*, 9074.
12. Austin, W. F.; Zhang, Y.; Danheiser, R., *Org. Lett.* **2005**, *7*, 3905.
13. Sun, J.; Kozmin, S. A., *J. Am. Chem. Soc.* **2005**, *127*, 13512.
14. McNulty, J.; Mao, J., *Tetrahedron Lett.* **2002**, *43*, 3857.

2-Trimethylsilyl-1,3-benzothiazole

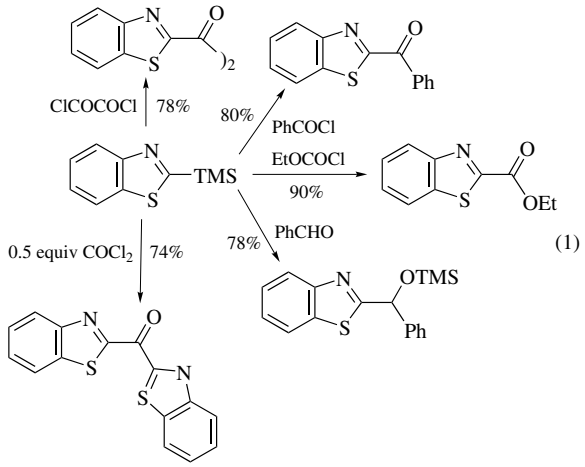


[32137-73-8] $C_{10}H_{13}NSSi$ (MW 207.40)
InChI = 1/C10H13NSSi/c1-13(2,3)10-11-8-6-4-5-7-9(8)12-10/h4-7H,1-3H3
InChIKey = MNXBVXVIRAIAEG-UHFFFAOYAY

(silyl heterocycle that reacts with a variety of electrophiles)

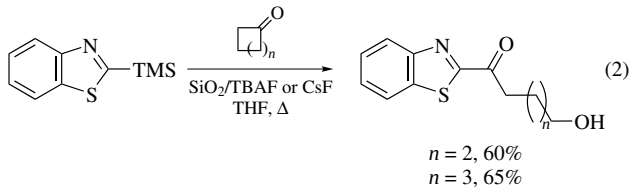
Physical Data: bp 139 °C/15 mmHg; n_D^{25} = 1.57.
Solubility: sol all organic solvents.
Analysis of Reagent Purity: NMR.
Purification: vacuum distillation.
Handling, Storage, and Precautions: can be stored indefinitely in the refrigerator in the absence of moisture.

Reaction with Carbon Electrophiles. The ability of this reagent to transfer the benzothiazol-2-yl unit to carbon electrophiles, is demonstrated by reactions with aldehydes, acyl halides, and chloroformates that give trimethylsilyl carbinols, ketones, and esters (eq 1).[1]



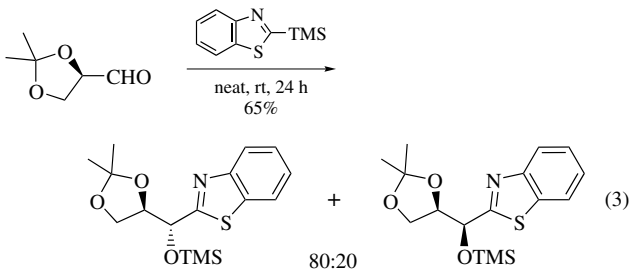
The reaction with benzaldehyde is performed under a dry nitrogen atmosphere at 160 °C for 40 h; acyl halides and ethyl chloroformate react under milder reaction conditions. The reaction of 2 equiv of 2-trimethylsilyl-1,3-benzothiazole and phosgene[2] occurs at 0 °C and provides a bis-heteroaryl ketone; oxalyl chloride[2] is converted to the (benzothiazol-2-yl)-substituted diketone. In these reactions the use of the corresponding stannylated derivative

leads in several cases to complex product mixtures. The reactivity toward electrophiles is increased in the presence of a catalytic amount of fluoride ion.[3] The easy F^--catalyzed desilylation, promoted by cesium fluoride or SiO_2-supported tetrabutylammonium fluoride, allows reaction with a wider range of electrophiles such as saturated lactones (eq 2). δ-Valero- and ε-caprolactone react smoothly under F^- catalysis, affording the corresponding keto alcohols from acyl–oxygen bond cleavage. Ring size effects are also seen; reaction of β-propiolactone fails because of ring opening and polymerization, whereas γ-butyrolactone gives only modest conversion yields (15%). With cyclohexen-2-one as an electrophile, conjugated addition of the benzothiazol-2-yl carbanion occurs, with formation of the Michael adduct.



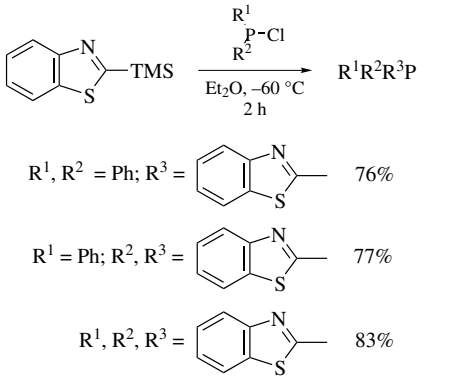
(2)

Stereoselective Additions. The addition of 2-trimethylsilyl-1,3-benzothiazole to α-asymmetric aldehydes proceeds[4] under mild conditions in good chemical yield and with significant stereoselectivity. In particular, the reaction with D-glyceraldehyde gives the *anti*-isomer with 80% diastereomeric purity (eq 3). The diastereoselectivity appears to vary depending on the azole nucleophile. Reaction of 2-lithiobenzothiazole with the same aldehyde (Et_2O, −78 °C) shows a complete lack of stereoselectivity. Unmasking the formyl group, using suitable procedures from the literature,[5a,b] allows 2-trimethylsilyl-1,3-benzothiazole to be used as a formyl anion equivalent in the diastereoselective synthesis of α-hydroxy carbonyl derivatives.



(3)

Synthesis of Heterocyclic-substituted Tertiary Phosphines. Electrophilic cleavage of the C–Si bond of 2-trimethylsilyl-1,3-benzothiazole by phosphorus(III) chloride, $PhPCl_2$, and Ph_2PCl, affords the tris-, bis-, and mono(benzothiazol-2-yl)phosphines in good yields (eq 4). The procedure involves the electrophilic cleavage of the C–Si bond and formation of a C–P bond.[6] The reactions are conducted neat and the phosphorus derivatives appear quite air-stable even at room temperature. Attempts to prepare tris(benzothiazol-2-yl)phosphines by reaction of the corresponding heteroaryl organolithium reagent and PCl_3 were unsuccessful.



(4)

1. Pinkerton, F. H.; Thames, S. F., *J. Heterocycl. Chem.* **1971**, *8*, 257.
2. Jutzi, P.; Gilge, U., *J. Heterocycl. Chem.* **1983**, *20*, 1011.
3. Ricci, A.; Fiorenza, M.; Grifagni, M. A.; Bartolini, G., *Tetrahedron Lett.* **1982**, *23*, 5079.
4. Dondoni, A.; Fogagnolo, M.; Medici, A.; Pedrini, P., *Tetrahedron Lett.* **1985**, *26*, 5477.
5. (a) Altman, L. J.; Richheimer, S. L., *Tetrahedron Lett.* **1971**, 4709. (b) Chikasita, H.; Ishibaba, M.; Ori, K.; Itoh, K., *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3637.
6. Moore, S. S.; Whitesides, G. M., *J. Org. Chem.* **1982**, *47*, 1489.

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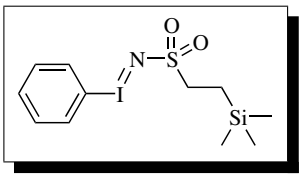
[*N*-(2-(Trimethylsilyl)ethanesulfonyl)-imino]phenyliodane



[236122-13-7] $C_{11}H_{18}INO_2SSi$ (MW 383.32)
InChI = 1/C11H18INO2SSi/c1-17(2,3)10-9-16(14,15)13-12-11-7-5-4-6-8-11/h4-8H,9-10H2,1-3H3
InChIKey = PDQYQRCBDUNXBI-UHFFFAOYAN

(iodine(III) reagent used as a nitrogen atom source in the transition-metal catalyzed aziridination of olefins or in the sulfoximination of sulfoxides)[1,2]

Alternate Names: phenyl{[(2-(trimethylsilyl)ethyl)sulfonyl] amino} iodonium, inner salt.

Physical Data: mp 84–85.5 °C.[3]

Solubility: slightly soluble in CH_2Cl_2, $CHCl_3$ (slow decomposition observed).

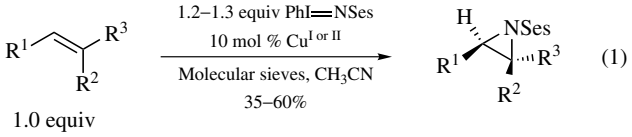
Form Supplied in: pale yellow solid. Typical impurities are $SesNH_2$ and PhI.

Analysis of Reagent Purity: ^1H NMR analysis of iminoiodane purity is unreliable since it is unstable and only slightly soluble in $CDCl_3$. Iodometric titration is possible. Another test of purity could be the use of the reagent in a standard aziridination applied to a five-molar excess of styrene.[4]

Preparative Methods: the protocol is adapted from the original synthesis of I-N ylides.[5] $SesNH_2$ (prepared by reaction of Ses-Cl[6] with concentrated aqueous ammonia at 0 °C in CH_3CN), KOH pellets (2.5 equiv), and $PhI(OAc)_2$ (1.0 equiv) are successively added to anhydrous methanol at 0 °C. After 3 h of stirring from 0 °C to rt, an expeditive work-up, described below, is followed. The mixture is diluted at 0 °C with freshly distilled CH_2Cl_2 and washed with ice water. After separation, the organic phase is dried over $MgSO_4$ and evaporated to dryness at room temperature. More reliable and practical now is the in situ generation of PhINSes from PhIO and $SesNH_2$.[7] This procedure is strongly recommended since the isolation of iminoiodinanes is particularly troublesome.

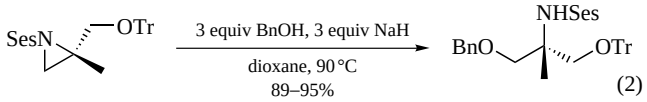
Handling, Storage, and Precautions: for optimal results, the reagent should be stored under argon at −20 °C. Irritating to skin. As with any hypervalent iodine reagent, caution is required while heating.

Copper-catalyzed Aziridination of Olefins. In the presence of a catalytic quantity of copper salts and activated 3 or 4 Å molecular sieves in acetonitrile, the title reagent (PhI=NSes) reacts with a wide range of alkenes, the stoichiometrically limiting component, to give the corresponding aziridines in 35–60% yield (eq 1).[3] Slightly better results are obtained when the iminoiodane is generated in situ from iodosylbenzene and $SesNH_2$,[7] while copper(I) salts, typically copper(I) trifluoromethanesulfonate and tetrakis(acetonitrile)copper(I) hexafluorophosphate, afford higher yields. The reactivity of PhI=NSes is thus comparable to that of [*N*-(*p*-toluenesulfonyl)imino]phenyliodane (PhI=NTs).[4]



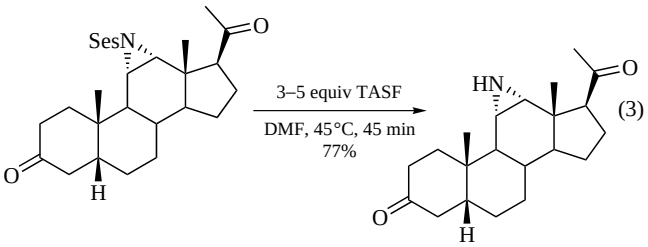
(1)

The resulting *N*-(Ses)aziridines are valuable synthetic intermediates. The electron-withdrawing character of the Ses-group allows ring opening of the aziridines by nucleophiles under mild conditions (eq 2),[3,8] as is the case with activated *N*-(Ns)aziridines prepared from [*N*-(*p*-nitrobenzenesulfonyl)imino]phenyliodane (PhI=NNs)[9] or *N*-(Ts)aziridines.



(2)

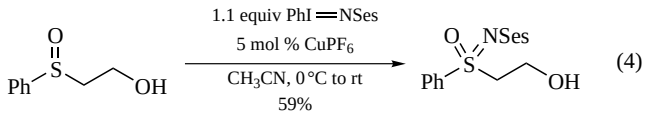
More significantly, the *N*-(Ses)aziridines can be deprotected without concomitant opening of the three-membered ring (eq 3)[3,10] by use of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), a fluoride anion source that is soluble in polar organic solvents at room temperature. Such clean deprotection also occurs with *N*-(Ts)aziridines by using reductive conditions, namely magnesium in methanol[11] or sodium naphthalenide.[12]



(3)

The direct copper-catalyzed iodosyl-mediated nitrogen transfer to olefins compares with the parent rhodium-catalyzed process that is made possible by the combination of iodosylbenzene diacetate, magnesium oxide, and sulfamates.[13] Other recent promising nitrene transfer methods involve the bromine-catalyzed aziridination of olefins using chloramine-T[14] and the direct electrochemical aziridination with *N*-aminophthalimide.[15]

Sulfoximination of Sulfoxides. Copper(I)- or copper(II)-catalyzed sulfoximination of sulfoxides[16,17] with PhI=NSes[18] leads to the corresponding *N*-(Ses)sulfoximines (eq 4) which could be cleanly deprotected to the free sulfoximines by use of tetrabutylammonium fluoride.



(4)

Related Reagents. [*N*-(*p*-Toluenesulfonyl)imino]phenyl iodane; [*N*-(*p*-Nitrobenzenesulfonyl)imino]phenyliodane.

1. Müller, P., In *Advances in Catalytic Processes*; Doyle, M. P., ed.; JAI Press: Greenwich, CT, 1997, p 113.
2. Zhdankin, V. V.; Stang, P. J., *Chem Rev.* **2002**, *102*, 2523.
3. Dauban, P.; Dodd, R. H., *J. Org. Chem.* **1999**, *64*, 5304.
4. Evans, D. A.; Faul, M. M.; Bilodeau, M. T., *J. Am. Chem. Soc.* **1994**, *116*, 2742.
5. Yamada, Y.; Yamamoto, T.; Okawara, M., *Chem. Lett.* **1975**, 361.
6. Weinreb, S. M.; Chase, C. E.; Wipf, P.; Venkatraman, S., *Org. Synth.* **1998**, *75*, 161.
7. Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H., *J. Am. Chem. Soc.* **2001**, *123*, 7707.
8. Wipf, P.; Venkatraman, S.; Miller, C. P., *Tetrahedron Lett.* **1995**, *36*, 3639.
9. Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G., *Tetrahedron Lett.* **1997**, *38*, 6897.
10. Di Chenna, P. H.; Dauban, P.; Ghini, A.; Baggio, R.; Garland, M. T.; Burton, G.; Dodd, R. H., *Tetrahedron* **2003**, *59*, 1009.
11. Alonso, D. A.; Andersson, P. G., *J. Org. Chem.* **1998**, *63*, 9455.
12. Bergmeier, S. C.; Seth, P. P., *Tetrahedron Lett.* **1999**, *40*, 6181.
13. Guthikonda, K.; Du Bois, J., *J. Am. Chem. Soc.* **2002**, *124*, 13672.
14. Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B., *J. Am. Chem. Soc.* **1998**, *120*, 6844.
15. Siu, T.; Yudin, A. K., *J. Am. Chem. Soc.* **2002**, *124*, 530.
16. Bolm, C.; Muniz, K.; Aguilar, N.; Kesselgruber, M.; Raabe, G., *Synthesis* **1999**, 1251.

17. Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M., *Synlett* **2002**, 116.
18. Cren, S.; Kinahan, T. C.; Skinner, C. L.; Tye, H., *Tetrahedron Lett.* **2002**, *43*, 2749.

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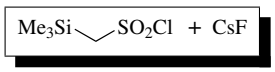
(Trimethylsilyl)methanesulfonyl Chloride–Cesium Fluoride



($Me_3SiCH_2SO_2Cl$)
[18143-34-5] $C_4H_{11}ClO_2SSi$ (MW 186.76)
InChI = 1/C4H11ClO2SSi/c1-9(2,3)4-8(5,6)7/h4H2,1-3H3
InChIKey = BFUMGFNGDCUBSH-UHFFFAOYAW
(CsF)
[13400-13-0] CsF (MW 151.91)
InChI = 1/Cs.FH/h;1H/q+1;/p-1/fCs.F/h;1h/qm;-1
InChIKey = XJHCXCQVJFPJIK-BCEBLLACCO

(source of 'free' sulfene in solution;[1] source of silylated sulfene[8])

Physical Data: $Me_3SiCH_2SO_2Cl$ is a colorless liquid, bp 50–52 °C/0.6 mmHg, 57 °C/1 mmHg; mp 18 °C, n_D^{20} 1.4700,[3] 1.4680.[7a] See also cesium fluoride.

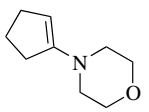
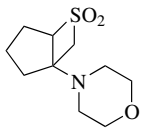
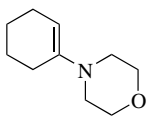
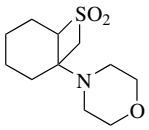
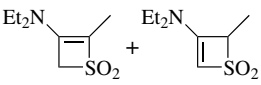
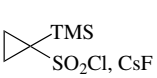
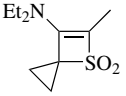
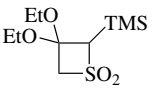
Solubility: acetonitrile is the preferred solvent due to solubility of CsF and absence of hydrogen bonding; $Me_3SiCH_2SO_2Cl$ is soluble in most organic solvents.

Preparative Methods: $Me_3SiCH_2SO_2Cl$ is: (1) formed in 58% isolated yield via reaction of (chloromethyl)trimethylsilane with thiourea in ethanol followed by concentration and chlorination in water, extraction, and distillation;.[2] (2) formed in 63% isolated yield by peracetic acid oxidation of (trimethylsilyl)methanethiol followed by treatment with phosphorus(V) chloride;[2] (3) formed in 84% yield through reaction of Me_3SiCH_2Cl with magnesium followed by sequential reaction of the Grignard reagent with sulfur dioxide followed by chlorine;[3] and (4) formed in 53% yield through reaction of tetramethylsilane with sulfuryl chloride.[7a]

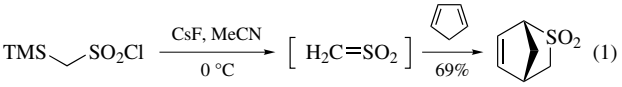
Handling, Storage, and Precautions: like most sulfonyl chlorides, the title compound hydrolyzes slowly to produce HCl and therefore should be kept dry. The byproduct of hydrolysis is hexamethyldisiloxane. Hydrolysis is very rapid with 5% NaOH solution.[7a]

Formation of Sulfene Adducts. A widely used procedure for the generation of sulfene involves the treatment of methanesulfonyl chloride with triethylamine. While adducts of sulfene,

Table 1 Sulfene adducts from (trimethylsily)methanesulfony chloride and related compounds

Substrate	Reagent	Product	Yield (%)	Ref.
	$TMSCH_2SO_2CL,CsF$		69	1
	$(TMSCH_2SO_2)_2O,CsF$		75	2
	$(TMSCHEtSO_2)_2O,CsF$		76	2
	$TMSCH_2SO_2CL,CsF$		81	1
	$TMSCH_2SO_2CL,CsF$		65	1
$MeC{\equiv}CNt_2$	$TMSCH_2SO_2CL,CsF$	 1:1	90	1
$MeC{\equiv}CNEt_2$			56	5
$H_2C{=}C(OEt)_2$	$TMSCH_2SO_2CL,Et_3N$		95	8

generated by this route, can usually be isolated in satisfactory yield, the amine or its acid salt may isomerize or decompose base- or acid-sensitive reaction partners. Furthermore, the interpretation of reaction mechanisms can sometimes be complicated by the presence of the amine. Thus the amine may form a complex with sulfene prior to its reaction with other substrates. In the presence of a fluoride ion source such as CsF, $Me_3SiCH_2SO_2Cl$ undergoes fluorodesilylation to give sulfene which can be trapped with cyclopentadiene giving the Diels–Alder adduct 2-thiabicyclo[2.2.1] hept-5-ene 2,2-dioxide in 69% yield (eq 1). The same reaction fails when mesyl chloride–triethylamine is used as a sulfene source. Additional examples of sulfene adducts, including a number of thietane *S,S*-dioxides, formed from $Me_3SiCH_2SO_2Cl$ are given in Table 1.[1,2,5,8] This procedure can also be used with homologs of $Me_3SiCH_2SO_2Cl$ such as $Me_3SiCHRSO_2Cl$, $(Me_3SiCH_2SO_2)_2O$, $(Me_3SiCHRSO_2)_2O$, $Me_3SiCH_2S(O)Cl$,[4] and 1-(trimethylsilyl) cyclopropanesulfonyl chloride.[5,6] If $Me_3SiCH_2SO_2Cl$ is treated with triethylamine in the presence of the electron-rich alkene ketene diethyl acetal, then the silylated sulfene trimethylsilylthioformaldehyde *S,S*-dioxide ($Me_3SiCH{=}SO_2$) is trapped.[8] The mechanism of hydrolysis of $Me_3SiCH_2SO_2Cl$ in the presence of KF has been studied.[3]



(1)

1. Block, E.; Aslam, M., *Tetrahedron Lett.* **1982**, *23*, 4203.
2. Block, E.; Wall, A., *J. Org. Chem.* **1987**, *52*, 809.
3. King, J. F.; Lam, J. Y. L., *J. Org. Chem.* **1993**, *58*, 3429.
4. Block, E.; Wall, A., *Tetrahedron Lett.* **1985**, *26*, 1425.
5. Block, E.; Schwan, A.; Dixon, D. A., *J. Am. Chem. Soc.* **1992**, *114*, 3492.
6. Block, E.; Aslam, M., *Tetrahedron* **1988**, *44*, 281.
7. (a) Cooper, G. D., *J. Org. Chem.* **1956**, *21*, 1214. (b) Baukov, Y. I.; Shipov, A. G.; Gorshkova, L. V.; Savost'yanova, I. A.; Kisin, A. V., *Zh. Obshch. Khim.* **1977**, *47*, 1538.
8. Shipov, A. G.; Kisin, A. V.; Baukov, Y. I., *J. Org. Chem. USSR (Engl. Transl.)* **1979**, 1022; Shipov, A. G.; Baukov, Y. I., *J. Org. Chem. USSR (Engl. Transl.)* **1979**, 1112.

Eric Block
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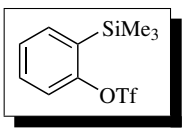
2-(Trimethylsilyl)phenyl Triflate



[88284-48-4] $C_{10}H_{13}F_3O_3SSi$ (MW 298.35)
InChI = 1/C10H13F3O3SSi/c1-18(2,3)9-7-5-4-6-8(9)16-17(14,15)10(11,12)13/h4-7H,1-3H3
InChIKey = XBHPFCIWRHJDCP-UHFFFAOYAH

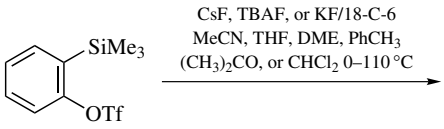
(reagent used as an aryne precursor in a variety of reactions)

Physical Data: bp 70 °C/2 mmHg; *d* 1.229 g mL^{-1}

Form Supplied in: liquid; widely available.

Handling, Storage, and Precautions: stable liquid. Incompatible with fluoride, hydroxide, or alkoxides, especially upon warming.

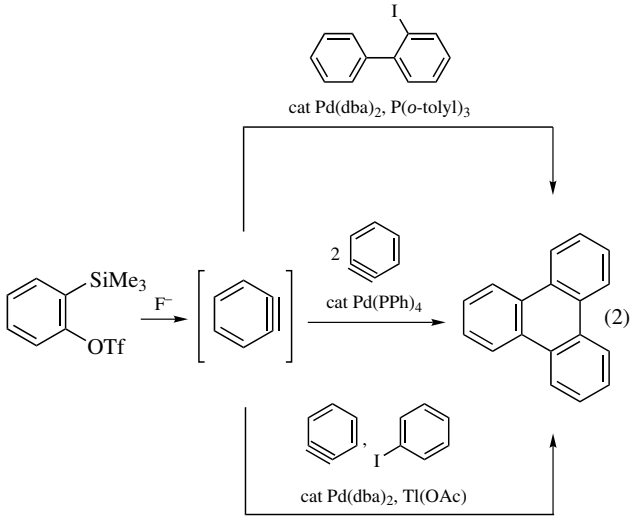
Kobayashi and co-workers introduced 2-(trimethylsilyl)phenyl triflate as an aryne precursor subject to benzyne formation without the need of a strong base.[1] Fluoride-induced desilylation and rapid elimination of the sulfonate provide efficient access to benzyne in acetonitrile at room temperature (eq 1). Other solvents such as THF, acetone, dichloromethane, DME, and toluene may be used, but such conditions may require heating for benzyne formation and frequently afford diminished yields. Preparation of the benzyne intermediate is even possible in protic media, albeit with decreased efficiency and limited applicability in subsequent reaction steps.[1]



(1)

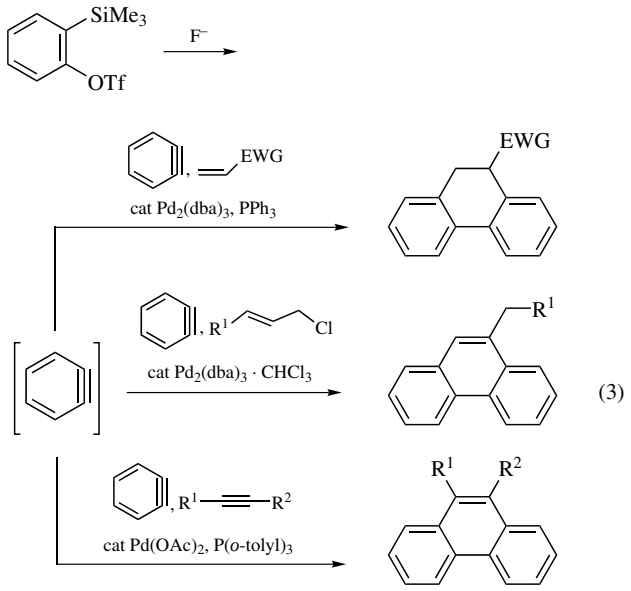
Various fluoride sources are employed for benzyne generation. Cesium fluoride or TBAF are most commonly used; however, the combination of potassium fluoride and 18-crown-6 also works well. The use of excess fluoride, typically 2 to 4 equiv, tends to provide superior results.

Polycyclic Arenes. Trimethylsilylphenyl triflates have found widespread use as benzyne precursors in the preparation of polycyclic arenes. Triphenylenes are made via palladium-catalyzed [2 + 2 + 2] cyclotrimerization of arynes,[2] by palladium-catalyzed annulation of the aryne and 2-halobiaryls,[3] or via carbopalladation/carbocyclization of arynes with substituted iodobenzenes (eq 2).[4] All three approaches furnish substituted triphenylenes in high reported yields. Substituted phenanthrenes or naphthalenes are similarly prepared using 2-(trimethylsilyl) phenyl triflate as an aryne precursor. Treatment of the reagent with fluoride, a palladium catalyst, and a deactivated alkene,[5] allyl halide,[6] or internal alkyne[7] provides 9-substituted or 9,



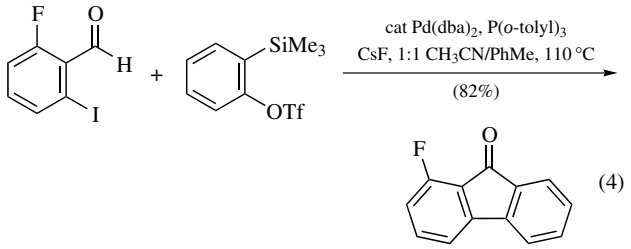
(2)

10-disubstituted phenanthrenes in moderate to good yields (eq 3). Substituted naphthalenes are created by reacting the aryne with alternate combinations of the listed reagents using specific palladium catalysts.[7,8] Aryl naphthalene lignans are attainable through a Pd-catalyzed [2 + 2 + 2] cocyclization of the aryne and diynes. This route has been used to synthesize lignan-containing natural products.[9] Extended fused polycyclic arenes are also accessible using related approaches.[10]



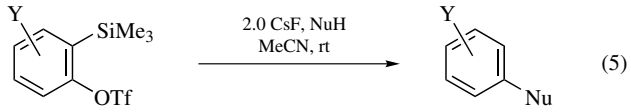
(3)

The palladium-catalyzed annulation of arynes, derived from 2-(trimethylsilyl)phenyl triflate, by 2-halobenzaldehydes provides variably substituted fluoren-9-ones in good yields (eq 4).[11] Catalytic dicobalt octacarbonyl under CO pressure furnishes anthraquinones in the presence of the aryne derived from 2-(trimethylsilyl)phenyl triflate.[12]



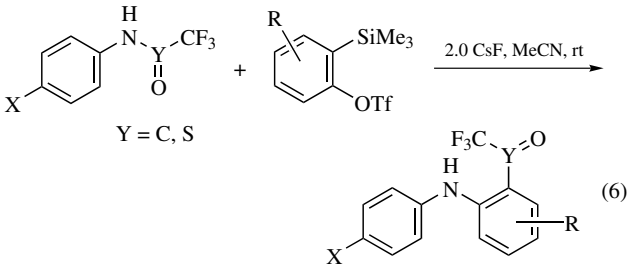
(4)

Heteroatom Arylation. Benzynes have a proven history as superior electrophiles in heteroatom arylation reactions. As such, aryne generation from 2-(trimethylsilyl)phenyl triflates offers particularly convenient access to anilines, anisoles, thioanisoles, etc. at ambient temperature using easily administered fluoride sources. The *N*-arylation of amines, azaarenes, or sulfonamides proceeds in uniformly excellent yields via this approach. Phenols and arenecarboxylic acids are also suitable nucleophiles, providing biaryl ethers or phenyl esters (eq 5).[13] Trifluoromethylamides and sulfinamides serve as both nucleophiles and acylating agents under these conditions to afford 2-trifluoroacylanilines or 2-trifluoromethylsulfoxyanilines, respectively (eq 6).[14] Similarly, cyclic ureas provide rapid access to simple benzodiazepines (eq 7) and benzodiazocines.

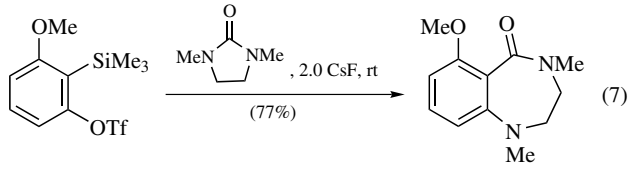


(5)

Nu = NR_2, HNR, $ArSO_2NR$
OAr, O_2CAr, SAr



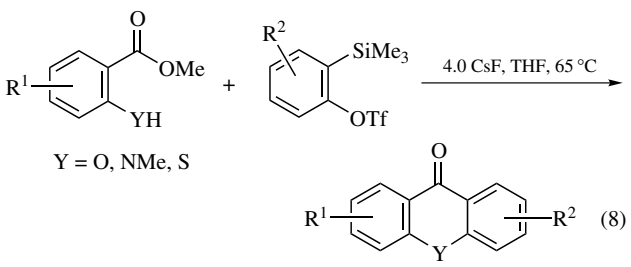
(6)



(7)

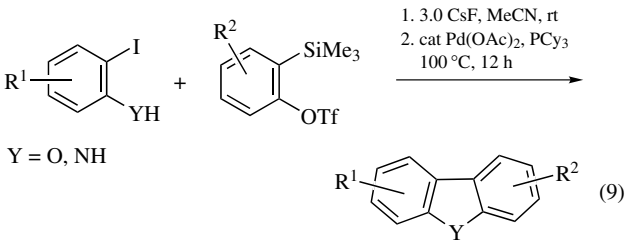
Acyclic ureas give 2-aminobenzamides in moderate yields via an analogous benzyne arylation/acylation pathway.[15] Heating azaarenes with 2-(trimethylsilyl)phenyl triflate and CsF in a cyanocarbon solvent furnishes 2-cyanomethyl-*N*-aryl azacycles in good yields. The nitriles must possess a hydrogen at the 2-position and are deprotonated by the zwitterionic arylation intermediate prior to addition by the azaarenium moiety (Reissert-type reaction).[16] Palladium-catalyzed disilylation[17] or distannylation[18] of the aryne is possible by the treatment of various 2-(trimethylsilyl) phenyl triflates with KF/18-crown-6, *tert*-octyl isocyanide ligand, and a disilane or distannane. This method is also amenable to the preparation of the 2,2′-heterosubstituted biphenyls via employment of an alternate Pd^0-ligand.[19]

Heteroarenes and Benzannulated Heterocycles. The heteroatom arylation methods involving 2-(trimethylsilyl)phenyl triflates have been extended to the preparation of heterocycles. Acridones, xanthones, and thioxanthones are readily obtained by reacting methyl 2-aminobenzoate, methyl salicylate, or methyl thiosalicylate, respectively, with the aryne generated from 2-(trimethylsilyl)phenyl triflate (eq 8).[20] The aryne is also used to prepare various benzannulated heterocycles via a three-component coupling process where at least one other component is an imine or carbonyl compound. This procedure provides simple entry to racemic substituted benzoiminofurans,[21] 2-iminoisoindolines,[22] 9-arylxanthenes,[23] or benzoxazinones.[24] Carbazoles or dibenzofurans are attained in high yields via the coupling of



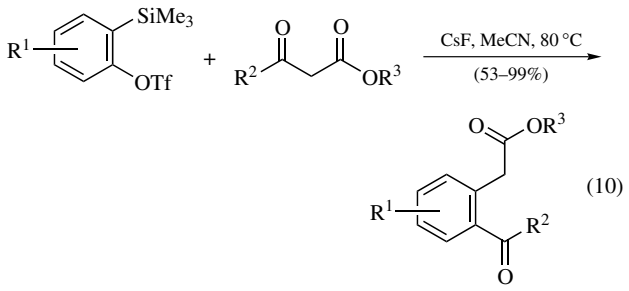
(8)

2-iodoanilines or 2-iodophenols with 2-silylphenyl triflates followed by intramolecular palladium-catalyzed cyclization (eq 9).[25]



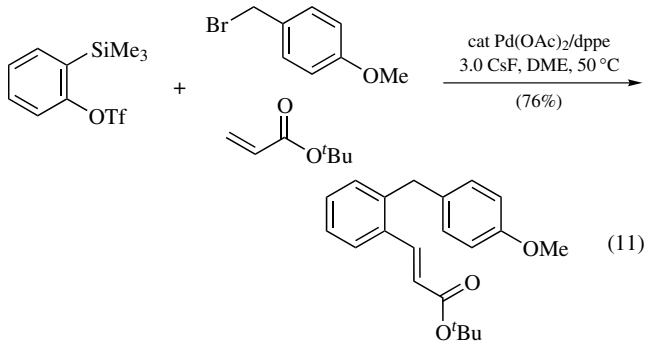
(9)

Carbon Arylations. Active methylene compounds are susceptible to the arylation/acylation reactions described above. Treatment of β-diketones, β-ketoesters, or dialkyl malonates with a 2-(trimethylsilyl)phenyl triflate and fluoride affords the aryl alkylation–acylation products in moderate to high yields (eq 10).[26] β-Ketonitriles and 2-cyanoformates are also compatible with this process, furnishing 2-cyanomethylphenones or alkyl benzoates, respectively.[27] A transition-metal-free regioselective coupling between pyridine *N*-oxides and arynes gives 3-(2-hydroxyaryl)-pyridines in good to excellent yields. This approach avoids the low yields and regioisomeric mixtures commonly observed in the preparation of such heterocycles.[28] The benzyne generated from 2-(trimethylsilyl)phenyl triflate may also be copolymerized with pyridine to give alternating *o*-phenylene and 2,3-dihydropyridine containing copolymers.[29]



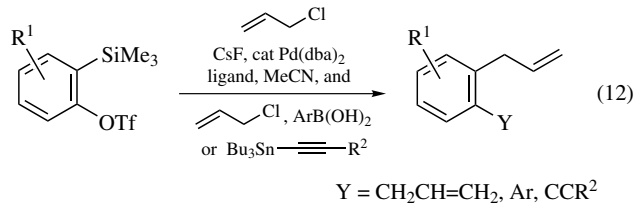
(10)

A three component coupling reaction involving carbopalladation of the aryne followed by a Heck coupling with *tert*-butyl acrylate affords *ortho*-substituted cinnamic acids in good yields (eq 11).[30] An ene reaction between the aryne, generated in THF at room temperature, and an alkyne creates allenylbenzenes in moderate yields.[31] The reaction of π-allylpalladium species with the benzyne created from 2-(trimethylsilyl)phenyl triflate provides access to several types of products in multicomponent



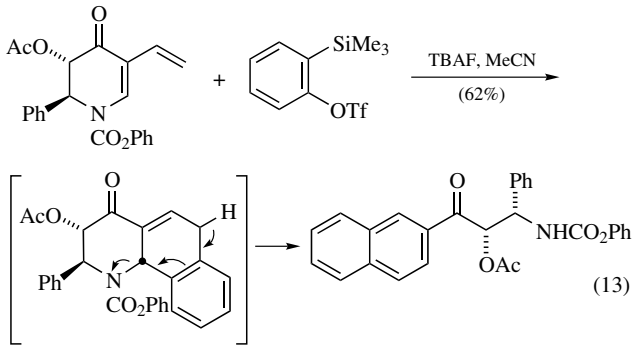
(11)

coupling reactions. For example, bis(π-allylpalladium) reagents afford 1,2-diallylated benzenes in moderate yields,[32] while allylation followed by Stille coupling with alkynylstannanes[33] or Suzuki–Miyaura coupling with arylboronic acids[34] yields 1-allyl-2-alkynylbenzenes or 2-allylbiphenyls, respectively (eq 12).



(12)

The benzyne created from 2-(trimethylsilyl)phenyl triflate was used in a highly diastereoselective aryne Diels–Alder reaction with a diene bearing Oppolzer's sultam. This approach to *cis*-functionalized 1,4-dihydronaphthalenes was reportedly the first aryne Diels–Alder reaction to provide enantioenriched cycloadducts.[35] An unusual route to β-aminoketones involves the treatment of 2-(trimethylsilyl)phenyl triflate with TBAF and an asymmetric vinyldihydropyridone. The resultant aryne Diels–Alder cycloadduct undergoes aromatization/elimination to create the *N*-acyl-β-aminoketone (eq 13).[36] This method was featured in a multistep synthesis of an unnatural α-amino acid.



(13)

Related Reagents. (Phenyl)-[*o*-(trimethylsilyl)phenyl]-iodonium Triflate; 2-Diazoniobenzenecarboxylate.

1. Himeshima, Y.; Sonoda, T.; Kobayashi, H., *Chem. Lett.* **1983**, 1211.
2. Peña, D.; Escadero, S.; Pérez, D.; Guitián, E., *Angew. Chem., Int. Ed.* **1998**, *37*, 2659.
3. Liu, Z.; Larock, R. C., *J. Org. Chem.* **2007**, *72*, 223.
4. Thatai Jayanth, T.; Cheng, C.-H., *Chem. Commun.* **2006**, 894.
5. Quintana, I.; Boersma, A. J.; Peña, D.; Pérez, D.; Guitián, E., *Org. Lett.* **2006**, *8*, 3347.
6. Yoshikawa, E.; Radhakrishnan, K.V.; Yamamoto, Y., *J. Am. Chem. Soc.* **2000**, *122*, 7280.
7. (a) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L., *J. Org. Chem.* **2000**, *65*, 6944. (b) Radhakrishnan, K. V.; Yoshikawa, E.; Yamamoto, Y., *Tetrahedron Lett.* **1999**, *40*, 7533.
8. Hsieh, J.-C.; Cheng, C.-H., *Chem. Commun.* **2005**, 2459.
9. Sato, Y.; Tamura, T.; Mori, M., *Angew. Chem., Int. Ed.* **2004**, *43*, 2436.
10. (a) Thatai Jayanth, T.; Jeganmohan, M.; Cheng, C.-H., *J. Org. Chem.* **2004**, *69*, 8445. (b) Romero, C.; Peña, D.; Pérez, D.; Guitián, E., *Chem. Eur. J.* **2006**, *12*, 5677.
11. Zhang, X.; Larock, R. C., *Org. Lett.* **2005**, *7*, 3973.

12. Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S., *J. Am. Chem. Soc.* **2001**, *123*, 12686.
13. Liu, Z.; Larock, R. C., *J. Org. Chem.* **2006**, *71*, 3198.
14. Liu, Z.; Larock, R. C., *J. Am. Chem. Soc.* **2005**, *127*, 13112.
15. Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T., *Angew. Chem., Int. Ed.* **2002**, *41*, 3247.
16. Jeganmohan, M.; Cheng, C.-H., *Chem. Commun.* **2006**, 2454.
17. Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A., *Organometallics* **2005**, *24*, 156.
18. Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A., *Angew. Chem., Int. Ed.* **2004**, *43*, 5052.
19. Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A., *Chem. Commun.* **2005**, 5678.
20. Zhao, J.; Larock, R. C., *J. Org. Chem.* **2007**, *72*, 583.
21. Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A., *Angew. Chem., Int. Ed.* **2004**, *43*, 3935.
22. Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A., *Tetrahedron Lett.* **2004**, *45*, 8659.
23. Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A., *Org. Lett.* **2004**, *6*, 4049.
24. Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A., *J. Am. Chem. Soc.* **2006**, *128*, 11040.
25. Liu, Z.; Larock, R. C., *Tetrahedron* **2007**, *63*, 347.
26. (a) Tambar, U. K.; Stoltz, B. M., *J. Am. Chem. Soc.* **2005**, *127*, 5340. (b) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A., *Chem. Commun.* **2005**, 3292.
27. Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A., *Tetrahedron Lett.* **2005**, *46*, 6729.
28. Raminelli, C.; Liu, Z.; Larock, R. C., *J. Org. Chem.* **2006**, *71*, 4689.
29. Ihara, E.; Kurokawa, A.; Koda, T.; Muraki, T.; Itoh, T.; Inoue, K., *Macromolecules* **2005**, *38*, 2167.
30. Henderson, J. L.; Edwards, A. S.; Greaney, M. F., *J. Am. Chem. Soc.* **2006**, *128*, 7426.
31. Thatai Jayanth, T.; Masilamani, J.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H., *J. Am. Chem. Soc.* **2006**, *128*, 2232.
32. Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y., *Tetrahedron Lett.* **2000**, *41*, 729.
33. Jeganmohan, M.; Cheng, C.-H., *Org. Lett.* **2004**, *6*, 2821.
34. Thatai Jayanth, T.; Jeganmohan, M.; Cheng, C.-H., *Org. Lett.* **2005**, *7*, 2921.
35. Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M., *J. Am. Chem. Soc.* **2005**, *127*, 15028.
36. Comins, D. L.; Kuethe, J. T.; Miller, T. M.; Février, F. C.; Brooks, C. A., *J. Org. Chem.* **2005**, *70*, 5221.

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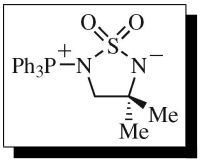
Triphenylphosphonium 3,3-Dimethyl-1,2,5-thiadiazolidine 1,1-Dioxide



[155632-33-0] $C_{22}H_{23}N_2O_2PS$ (MW 428.494)

InChI = 1/C22H23N2O2PS/c1-22(2)18-24(28(25,26)23-22)27(19-12-6-3-7-13-19,20-14-8-4-9-15-20)21-16-10-5-11-17-21/h3-17H,18H2,1-2H3

InChIKey = SLLNLUKIISRUKV-UHFFFAOYAX

(reagent for mediating Mitsunobu-like processes;[1] a convenient alternative to DEAD-triphenylphosphine system)

Physical Data: mp 169–172 °C (CH_2Cl_2–MeCN; decomposition).

Solubility: soluble in DMSO, CH_2Cl_2, $CHCl_3$; limited solubility in THF, toluene, Et_2O.

Form Supplied in: not commercially available. White solid.

Analysis of Reagent Purity: ^{1}H-NMR, ^{31}P-NMR, elemental analysis.

Preparative Methods: the title reagent can be prepared in quantitative yield by addition of DEAD (1 equiv) to a solution of 3,3-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide (1 equiv)[2] and triphenylphosphine (1 equiv) in THF at room temperature.[1] 3,3-Dimethyl-1,2,5-thiadiazolidine-1,1-dioxide can be prepared in high yield by reaction of sulfamide and 1,2-diamino-2-methylpropane in anhydrous pyridine.

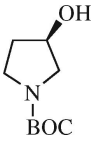
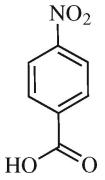
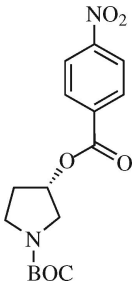
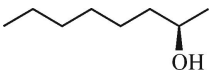
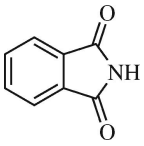
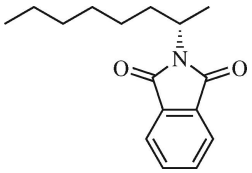
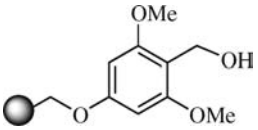
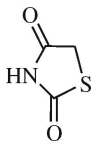
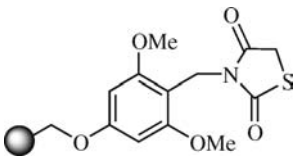
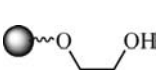
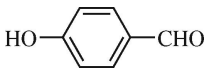
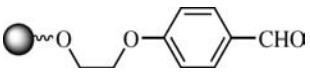
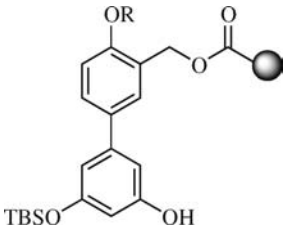
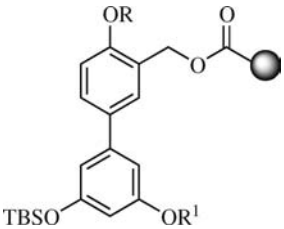
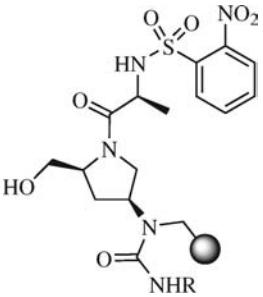
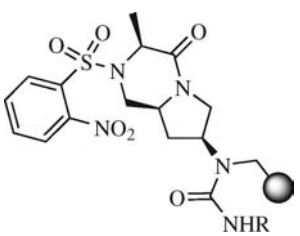
Purity: preparation of the reagent as above affords material of high purity with no need for further purification. Recrystallization can be achieved from CH_2Cl_2–MeCN.

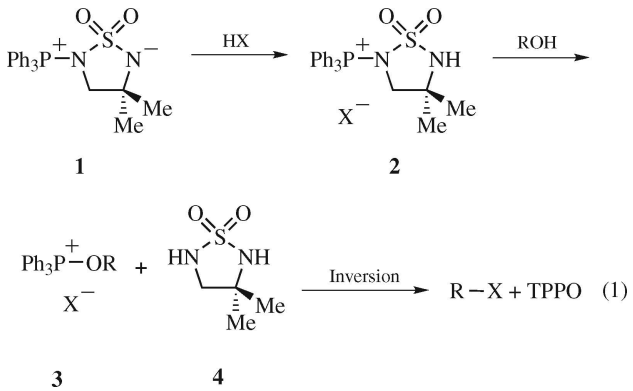
Handling, Storage, and Precautions: the compound is hydrolytically unstable to acid, decomposing on silica gel to triphenylphosphine oxide and 3,3-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide, but can be stored in the solid state at room temperature, under nitrogen, for several months without significant degradation. ^{1}H-NMR experiments in $CDCl_3$ may be misleading for purity check due to presence of DCl/HCl/H_2O.

Mitsunobu-like Processes. Triphenylphosphonium 3,3-dimethyl-1,2,5-thiadiazolidine 1,1-dioxide (**1**) can be conveniently utilized as a stable source of [Ph_3P^+] in the promotion of Mitsunobu-like processes. By analogy with the betaine generated by reaction of DEAD and triphenylphosphine, protonation of zwitterionic species **1** by an acidic component HX generates ion pair **2** which on subsequent reaction with an alcohol (ROH) affords oxyphosphonium species (**3**) and 3,3-dimethyl-1,2,5-thiadiazolidine-1,1-dioxide (**4**). Finally, S_N2 displacement reaction, occurring with Walden inversion of the alcohol stereochemistry, leads to the coupled product R–X and triphenylphosphine oxide (TPPO) (eq 1).

Reagent **1** has been utilized to promote the couplings of alcohols and carboxylic acids,[1] phenols,[3–7] phthalimide,[1] thiazolidinedione,[8] and sulphonamides.[9] The compound has gained

Table 1 Utility of betaine **1** in mitsunobu-like reactions

Substrate	HX	Conditions	Product	Yield	Ref.
				89%	1
		CH_2Cl_2, rt		80%	1
		CH_2Cl_2, rt		0.55 mmol/g loading	8
		CH_2Cl_2, rt		~100%	3
R^1OH		CH_2Cl_2/toluene 96-well format		~90%	4
		CH_2Cl_2/5% DMF		>90%	9



popularity as a preparatively useful reagent on Mitsunobu-like reactions on solid support, where advantages over conventional methodology have unfolded (e.g. convenient addition of one reagent rather than two, cleaner products).[3–5,8,9] Suitable solvents for the reaction include dichloromethane and toluene, and although the reagent is not usually soluble at the start of the process, a homogenous solution is obtained as the reaction proceeds (excluding resin in solid-phase syntheses). Cyclic sulfamide (**4**) is not extracted into Et_2O facilitating the isolation of coupled products. Illustrative examples of the above mentioned utilities are shown in Table 1.

Related Reagents. Triphenylphosphine; Diethyl Azodicarboxylate.[10]

1. Castro, J. L.; Matassa, V. G.; Ball, R. G., *J. Org. Chem.* **1994**, *59*, 2289.
2. Castro, J. L.; Baker, R.; Guiblin, A. R.; Hobbs, S. C.; Jenkins, M. R.; Rusell, M. G. N.; Beer, M. S.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J.; Graham, M. I.; Matassa, V. G., *J. Med. Chem.* **1994**, *37*, 3023.
3. Swayze, E. E., *Tetrahedron Lett.* **1997**, *38*, 8465.
4. Pavia, M. R.; Cohen, M. P.; Dilley, G. J.; Dubuc, G. R.; Durgin, T. L.; Forman, F. W.; Hediger, M. E.; Milot, G.; Powers, S. P.; Sucholeiki, I.; Zhou, S.; Hangauer, D. G., *Bioorg. Med. Chem.* **1996**, *4*, 659.
5. Daluge, S. M.; Jurgensen, C. H.; Martin, M. T.; Osterhout, M. H., World Patent Appl. WO 00/09707, 2000.
6. Dodge, J. A.; Glasebrook, A. L.; Lugar, C. W., European Patent Appl. EP 895989, 1999.
7. Carniato, D.; Gadek, T. R.; Gourvest, J. F.; Knolle, J.; Peyman, A.; Ruxer, J. M.; Bodary, S. C., World Patent Appl. WO 00/31036, 2000.
8. Brummond, K. M.; Lu, J., *J. Org. Chem.* **1999**, *64*, 1723.
9. Swayze, E. E., *Tetrahedron Lett.* **1997**, *38*, 8643.
10. Mitsunobu, O., *Synthesis* **1981**, 1.

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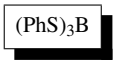
Merck Sharp & Dohme Research Laboratories, Harlow, UK

Triphenyl Thioborate



[1041-16-3] $C_{18}H_{15}BS_3$ (MW 338.35)

InChI = 1/C18H15BS3/c1-4-10-16(11-5-1)20-19(21-17-12-6-2-7-13-17)22-18-14-8-3-9-15-18/h1-15H

InChIKey = NAISZAOYZCJMTJ-UHFFFAOYAB

(conversion of esters and α,β-unsaturated esters into phenylthio esters,[1] and for formation of 1,3-bis(phenylthio)alkenes from aldehydes and ketones[2])

Alternate Names: phenyl thioborate; tris(phenylthio)borane.

Physical Data: pale yellow solid; mp 140–143 °C;[3] bp 196 °C/0.1 mmHg.[3]

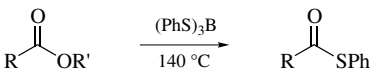
Solubility: sol benzene, ether, acetone.[4]

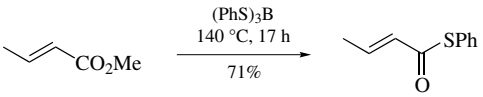
Preparative Methods: can be made from boron triiodide and diphenyl disulfide;[5] from thiophenol and boron trichloride;[6] from (phenylthio)borane trimer and thiophenol;[7] or from boron trisulfide and thiophenol.[2,8]

Purification: recrystallize from benzene[7] or distill in vacuo.[3]

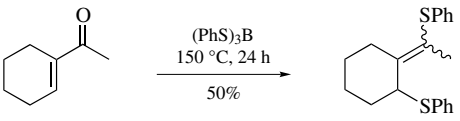
Handling, Storage, and Precautions: sensitive to moisture and should be stored in a desiccator. Can be weighed out quickly in air, if humidity is low, but best handled in a dry box.[2]

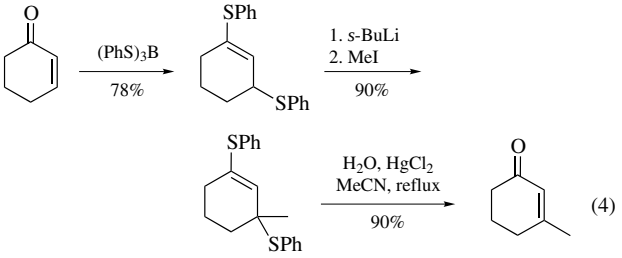
Conversion of Esters and α,β-Unsaturated Esters into Phenylthio Esters.[1] Esters are converted into phenylthio esters by heating with phenyl thioborate in refluxing xylene (140 °C) (eq 1), but the same transformation can be done at room temperature with phenyl thioaluminate. With the aluminum reagent, α,β-unsaturated esters give products contaminated with the β-(phenylthio) ester, but the boron reagent does not suffer from this disadvantage (eq 2).





Formation of 1,3-Bis(phenylthio)alkenes from Aldehydes and Ketones.[2] α,β-Unsaturated aldehydes and ketones form 1,3-bis(phenylthio)alkenes on treatment with phenyl thioborate (eq 3). The (phenylthio)alkenes are β-acyl vinyl anion equivalents (eq 4).





(4)

1. Cohen, T.; Gapinski, R. E., *Tetrahedron Lett.* **1978**, *45*, 4319.
2. Cohen, T.; Bennett, D. A.; Mura, A. J., Jr., *J. Org. Chem.* **1976**, *41*, 2506.
3. Finch, A.; Gardner, P. J.; Watts, G. B., *Trans. Faraday Soc.* **1967**, *63*, 1603.
4. Funk, H.; Koch, H. J., *Wiss. Z. Martin-Luther Univ.* **1959**, *8*, 1025 (*Chem. Abstr.* **1961**, *55*, 11 417h).
5. Siebert, W.; Rittig, F. R.; Schmidt, M., *J. Organomet. Chem.* **1970**, *22*, 511.
6. Young, D. M.; Anderson, C. D., *J. Org. Chem.* **1961**, *26*, 5235.
7. Shchegoleva, T. A.; Lavrinovich, L. I.; Bochkareva, M. N.; Mikhailov, B. M., *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1968**, 1780.
8. Brault, J.; Lalancette, J. M., *Can. J. Chem.* **1964**, *42*, 2903.

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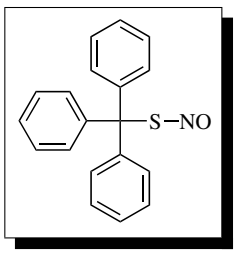
Trityl Thionitrite



[6316-86-5] $C_{19}H_{15}NOS$ (MW 305.40)

InChI = 1/C19H15NOS/c21-20-22-19(16-10-4-1-5-11-16, 17-12-6-2-7-13-17)18-14-8-3-9-15-18/h1-15H

InChIKey = YLEVRGODADSYBK-UHFFFAOYAH

(reagent used as precursor to Ph_3CS• and nitric oxide (NO))

Alternate Name: TTN.

Physical Data: mp 100–101 °C (decomp).

Solubility: soluble in CH_2Cl_2, $CHCl_3$, CCl_4; partially soluble in C_6H_6, ether; insoluble in methanol, ethanol.

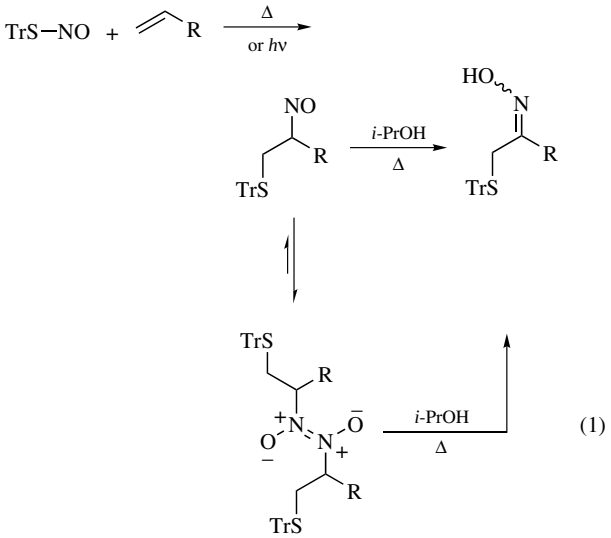
Preparative Methods: readily obtained as a green crystalline solid from triphenylmethylmercaptan and various nitrosating agents,[1–3] methods involving phase-transfer conditions appear to be the best.[3]

Purity: recrystallization from $CHCl_3$/ethanol.

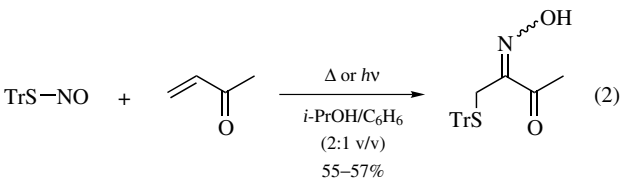
Handling, Storage, and Precaution: recrystallized and stored in the dark to prevent possible photolytic decomposition; decomposes thermally at ca. 110 °C and may be stored in a refrigerator for several days without detectable decomposition. Trityl thionitrite may be mutagenic[4] and skin contact should be avoided. Incompatible with alkenes, phosphines, thiols, amines, sulfoxides, and as well as various transition-metal salts and complexes.

As a crystalline and, therefore, chemically well-defined precursor to thiyl and NO radicals, each of which have biological relevance,[4] TTN has been characterized by ^{1}H,[5] ^{13}C,[5] ^{15}N,[6], and ^{17}O,[7] NMR spectroscopies as well as by X-ray crystallographic,[3] vibrational spectroscopic,[3] and electrical means.[3]

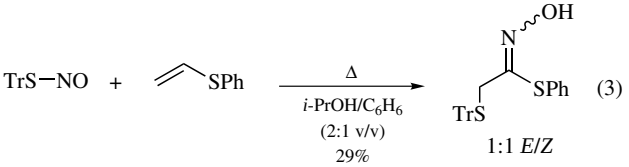
Homolytic Decomposition and Trapping of Product Radicals. Thermolysis of TTN affords, in a reversible fashion,[1] Ph_3CS• and NO with the former product capable of being 'spin trapped' by 5,5-dimethyl-1-Δ-pyrroline-*N*-oxide (DMPO) and the resulting conjugate characterized by ESR techniques.[8] Ph_3CS• can abstract hydrogen from a range of alkylarenes including, in order of increasing reactivity, toluene, ethylbenzene, tetralin, diphenylmethane, and 9,10-dihydroanthracene. The addition of the elements of TTN to alkenes can be carried out thermally or photochemically (eq 1).[9,10] The initially formed *C*-nitroso adducts often dimerize, but they also tautomerize to the corresponding oximes upon heating in the presence of isopropanol. A wide range of electron-rich and electron-deficient alkenes participate in this addition process which is often regioselective (eqs 2 and 3). With conjugated dienes TTN adds in a 1,4-fashion (eq 4).[10]



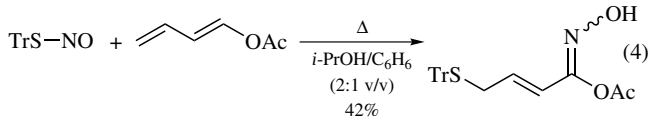
(1)



(2)



(3)

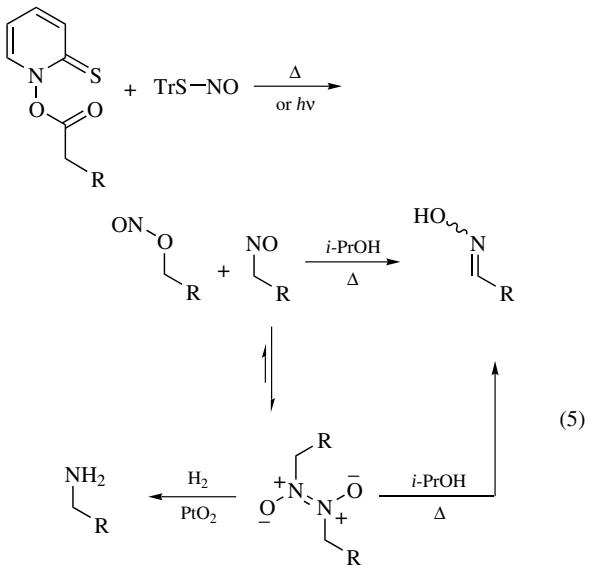


(4)

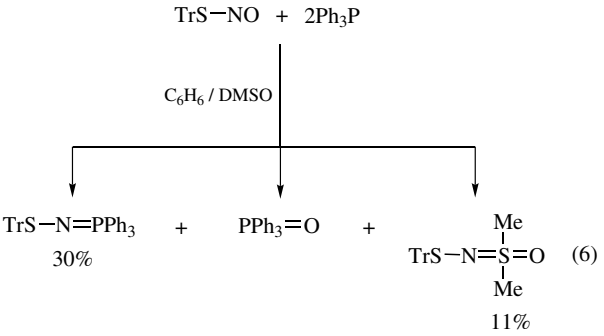
It has been suggested[10] that electron-transfer processes may be involved when electron-rich alkenes are substrates in these addition processes.

Decarboxylative Amination. Decarboxylative amination of carboxylic acids can be achieved by reacting the derived Barton esters with equimolar quantities of TTN under either thermal or photolytic conditions (eq 5).[5,11] The initially formed nitroso-compound couples, in situ, to give the *trans*-nitroso dimer along with small quantities of the corresponding nitrite ester (this by-product probably arises via reaction of the nitroso-compound with 2 equiv of NO followed by loss of nitrogen). The dimer can be converted into the oxime of the monomer in refluxing isopropanol or hydrogenated to give 2 equiv of the corresponding primary amine.[5,11]

Miscellaneous Reactions. Reaction of TTN with two molar equivalents of triphenylphosphine in benzene results in the formation of *N*-tritylthio-triphenylphosphinimine. When the same reaction is carried out in the presence of DMSO then *N*-tritylthio-dimethylsulfoximide is also obtained (eq 6). Tritythionitrene may be an intermediate in these conversions.[12]

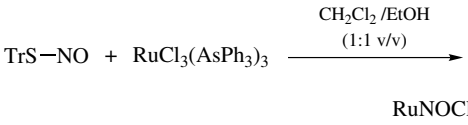


(5)



(6)

TTN has been used as an NO transfer agent in the formation of nitrosyl complexes of Ru, Rh, Ir, Co, Mo, and W (eq 7).[13] No yields have been reported for these reactions and the by-products have not been defined.



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1. Van Zwet, H.; Kooyman, E. C., *Recl. Trav. Chim. Pays-Bas.* **1968**, *87*, 45.
2. Cornélis, A.; Depaye, N.; Gerstmans, A.; Laszlo, P., *Tetrahedron Lett.* **1983**, *24*, 3103.
3. Arulsamy, N.; Bohle, D. S.; Butt, J. A.; Irvine, G. J.; Jordan, P. A.; Sagan, E., *J. Am. Chem. Soc.* **1999**, *121*, 7115.
4. Carter, M. H.; Josephy, P. D., *Biochem. Pharmacol.* **1986**, *35*, 3847.
5. Girard, P.; Guillot, N.; Motherwell, W. B.; Hay-Motherwell, R. S.; Potier, P., *Tetrahedron* **1999**, *55*, 3573.
6. Bonnett, R.; Holleyhead, R.; Johnson, B. L.; Randall, E. W., *J. Chem. Soc., Perkin Trans. 1* **1975**, 2261.
7. Dahn, H.; Péchy, P.; Flögel, R., *Helv. Chim. Acta.* **1994**, *77*, 306.
8. Josephy, P. D.; Rehorek, D.; Janzen, E. G., *Tetrahedron Lett.* **1984**, *25*, 1685.
9. Chandra, H.; Gowenlock, B. G.; Pfab, J., *J. Chem. Soc., Chem. Commun.* **1979**, 392.
10. Cavero, M.; Motherwell, W. B.; Potier, P., *Tetrahedron Lett.* **2001**, *42*, 4377.
11. Girad, P.; Guillot, N.; Motherwell, W. B.; Potier, P., *J. Chem. Soc., Chem. Commun.* **1995**, 2385.
12. Haake, M., *Tetrahedron Lett.* **1972**, 3405.
13. Pandey, D. S.; Agarwala, U. C., *Inorg. Chim. Acta.* **1989**, *159*, 197.

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General Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
BBN	borabicyclo[3.3.1]nonane
BCME	dis(chloromethyl)ether
BHT	butylated hydroxytoluene (2,6-di-*t*-butyl-*p*-cresol)
BINAL-H	2,2′-dihydroxy-1,1′-binaphthyl-lithium aluminum hydride
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2,2′-naphthol
bipy	2,2′-bipyridyl
BMS	borane–dimethyl sulfide
Bn	benzyl
Boc	*t*-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
Bs	brosyl (4-bromobenzenesulfonyl)
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	*n*-butyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
Cbz	benzyloxycarbonyl
CDI	*N*,*N*′-carbonyldiimidazole
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
Chx	=Cy
cod	cyclooctadiene
cot	cyclooctatetraene
Cp	cyclopentadienyl
CRA	complex reducing agent
CSA	10-camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
Cy	cyclohexyl
d	density
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	*N*,*N*′-diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBAD	di-*t*-butyl azodicarboxylate
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCME	dichloromethyl methyl ether
DDO	dimethyldioxirane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride
DIEA	=DIPEA
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
DIPEA	diisopropylethylamine
diphos	=dppe
DIPT	diisopropyl tartrate
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
dmg	dimethylglyoximato
DMPU	*N*,*N*′-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio) sulfonium tetrafluoroborate
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTBP	di-*t*-butyl peroxide
EDA	ethyl diazoacetate
EDC	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EDCI	=EDC
ee	enantiomeric excess
EE	1-ethoxyethyl
Et	ethyl
ETSA	ethyl trimethylsilylacetate
EWG	electron withdrawing group
Fc	ferrocenyl
Fmoc	9-fluorenylmethoxycarbonyl
fp	flash point
Hex	*n*-hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HOBt	l-hydroxybenzotriazole
HOBT	=HOBt
HOSu	*N*-hydroxysuccinimide
Im	imidazole (imidazolyl)
Ipc	isopinocampheyl
IR	infrared
KHDMS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LD_{50}	dose that is lethal to 50% of test subjects

LDA	lithium diisopropylamide
LDMAN	lithium 1-(dimethylamino)naphthalenide
LHMDS	=LiHMDS
LICA	lithium isopropylcyclohexylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
LTMP	=LiTMP
LTA	lead tetraacetate
lut	lutidine
m-CPBA	*m*-chloroperbenzoic acid
MA	maleic anhydride
MAD	methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)
MAT	methylaluminum bis(2,4,6-tri-*t*-butylphenoxide)
Me	methyl
MEK	methyl ethyl ketone
MEM	(2-methoxyethoxy)methyl
MIC	methyl isocyanate
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
MoOPH	oxodiperoxomolybdenum(pyridine)-(hexamethylphosphoric triamide)
mp	melting point
MPM	=PMB
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry; molecular sieves
MTBE	methyl *t*-butyl ether
MTM	methylthiomethyl
MVK	methyl vinyl ketone
n	refractive index
NaHDMS	sodium hexamethyldisilazide
Naph	naphthyl
NBA	*N*-bromoacetamide
nbd	norbornadiene (bicyclo[2.2.1]hepta-2,5-diene)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NORPHOS	bis(diphenylphosphino)bicyclo[2.2.1]-hept-5-ene
Np	=Naph
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pent	*n*-pentyl
Ph	phenyl
phen	1,10-phenanthroline
Phth	phthaloyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMDTA	*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylene-triamine
PPA	polyphosphoric acid
PPE	polyphosphate ester
PPTS	pyridinium *p*-toluenesulfonate
Pr	*n*-propyl
PTC	phase transfer catalyst/catalysis
PTSA	*p*-toluenesulfonic acid
py	pyridine
RAMP	(R)-1-amino-2-(methoxymethyl)pyrrolidine
rt	room temperature
salen	bis(salicylidene)ethylenediamine
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine
SET	single electron transfer
Sia	siamyl (3-methyl-2-butyl)
TASF	tris(diethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAD	=DBAD
TBAI	tetrabutylammonium iodide
TBAP	tetrabutylammonium perruthenate
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TBS	=TBDMS
TCNE	tetracyanoethylene
TCNQ	7,7,8,8-tetracyanoquinodimethane
TEA	triethylamine
TEBA	triethylbenzylammonium chloride
TEBAC	=TEBA
TEMPO	2,2,6,6-tetramethylpiperidinoxyl
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran; tetrahydropyranyl
Thx	thexyl (2,3-dimethyl-2-butyl)
TIPS	triisopropylsilyl
TMANO	trimethylamine *N*-oxide
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Tol	*p*-tolyl
TPAP	tetrapropylammonium perruthenate
TBHP	*t*-butyl hydroperoxide
TPP	tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
TTN	thallium(III) nitrate
UHP	urea–hydrogen peroxide complex
Z	=Cbz