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Preface

Heterocyclic molecules play a significant role in life processes and have played a major role in industrial developments of the last century, for instance in the field of dyes, pharmaceuticals, pesticides, polymers etc. They comprise not only some of the most interesting and biologically important natural products like alkaloids, carbohydrates, nucleic acids, and antibiotics but include many practical drugs and a large segment of known synthetic organic compounds. Hence scientists have devoted a great amount of effort to find optimal synthetic approaches to a variety of heterocyclic compounds.

Among the most successful and selective synthetic processes are cycloaddition reactions, since they involve simultaneous or sequential formation of two or more bonds often with a high degree of stereoselectivity and regioselectivity. For instance, 1,3 dipolar cycloadditions are electronically equivalent to Diels–Alder reactions and are among the most common 5-membered ring-forming systems. In addition they usually proceed with a high degree of stereo- and regio-control. It is therefore, not surprising that synthesis of many important classes of heterocycles, including those of useful biologically active molecules, have utilized cycloaddition steps in their formation. Furthermore, many heterocycles serve as intermediates in the synthesis of polyfunctional molecules.

In this volume we present five selected contributions by well-known authors, each an authority in his field. The first chapter deals with construction of isoxazolines (dihydroisoxazoles) via 1,3-dipolar cycloadditions of nitronates or of nitrile oxides generated from nitroalkanes. This includes inter- as well as intramolecular processes. Many of these heterocycles possess important synthetic and biological properties and are shown to lead to stereo- and regioselective introduction of multifunctional molecules such as amino alcohols, β-amino acids, aldols, nitriles, and others.

The second chapter is devoted to cycloadditions of azides, which comprise a highly versatile functional group. The chapter discusses both catalyzed and non-catalyzed (thermal) cycloadditions of azides to multiple bonds leading to many interesting classes of N-heterocycles. Both inter- and intramolecular azide cycloaddition reactions are featured. Furthermore, bioconjugation involving azides and their use in tagging of proteins, DNA as well as of living systems are highlighted.

Enantioselective 1,3-dipolar cycloadditions employing azomethine ylides and asymmetric catalysis are discussed in the next chapter. The formation of chiral non-racemic pyrrolidine derivatives via dipolar cycloadditions presents an important challenge that has been successfully overcome. The role of catalysis involving different metals is also highlighted.

Chapter 4 concerns the cycloaddition of carbonyl ylides generated from diazo carbonyl compounds and rhodium or copper catalysts. In this framework chemoselective and enantioselective transformations leading to the formation of various heterocycles such as tetrahydrofurans, oxazolidines, mesoionic and bicyclic compounds, alkaloids, and other natural products are described.

The final chapter deals with phosphorus ylides, in particular of phosphacumulenes, and their utilization in the synthesis of a number of heterocyclic ring systems including butenolides, tetramates, and macrolides. I want to thank all authors for their excellent presentations and their splendid cooperation.

This volume is dedicated with love to my children Lilly and Lawrence and their families.

Ramat Gan, February 2008 Alfred Hassner

Contents

Contents of Volume 13

Synthesis of Heterocycles via Cycloadditions II

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Isoxazolines from Nitro Compounds: Synthesis and Applications

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Abstract This paper reviews the construction of isoxazoline rings via 1,3-dipolar cycloaddition of nitrile oxides or nitronates, including silyl nitronates, generated from nitroalkanes, with alkenes. Recent studies on the mechanism and regiochemistry, inter- and intramolecular versions and asymmetric approaches to the cycloaddition are also dealt with in this review. A comparison of the nitrile oxide cycloaddition with silyl nitronate cycloaddition, especially their intramolecular versions, indicates the superiority of the silyl nitronate approach in providing the cycloadducts in greater yield and selectivity. Finally, various modes of cleavage of the isoxazoline ring to potentially useful synthetic intermediates are also discussed.

Keywords 1,3-dipolar cycloaddition · Isoxazolines · Nitrile oxide · Silyl nitronate

Abbreviations

BNO	Benzonitrile oxide
Boc	*tert*-butoxycarbonyl
B3LYP	Becke three-parameter hybrid density functional with correlation function of Lee, Yang and Parr with 20% of HF (Hartree–Fock) mixing
CCSD(T)	couple cluster method with single, double, and triple excitations
CM	Configuration mixing
DABCO	1,4-diazabicyclo[2.2.2]octane

DAST	Diethylaminosulphur trifluoride
13DC	1,3-dipolar cycloaddition
DFT	Density functional theory
DMAP	4-dimethylaminopyridine
DMTMM	(4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride)
FMO	Frontier molecular orbital
INOC	Intramolecular nitrile oxide-olefin cycloaddition
ISOC	Intramolecular silyl nitronate-olefin cycloaddition
MPI	3-methylenephthalimidine
MVK	Methyl vinyl ketone
TFA	Trifluoroacetic acid
TMS	Trimethyl silyl
TMEDA	Tetramethylethylenediamine

1 Introduction

Δ^2 –Isoxazolines (4,5-dihydroisoxazoles) **1** are one of the key *O*- and *N*-containing five-membered ring heterocycles which possess significant synthetic and biological applications [1–3]. Besides being precursors to many multi-functional synthetic intermediates such as β-hydroxyketones and nitriles, α, β-unsaturated ketones and oximes, γ-amino alcohols etc. [4, 5], isoxazolines **1** are excellent substrates for the synthesis of β-amino acids [6], *C*-disaccharides [7], imino/amino polyols, amino sugars [8] and novel aza-heterocycles [9, 10]. Isoxazoline-fused natural products, which include sugars and steroids, have been reported [11, 12]. A spiroisoxazoline moiety is an integral part of many biologically active natural products such as calafianin **2**, aerothionin **3a**, homoaerothionin **3b** and aerophobin **4** (Fig. 1) [13–16]. Applications of these *N*,*O*-heterocycles as key building blocks in the total synthesis of several natural and unnatural compounds such as β-lactam antibiotics, quinolizidine and indolizine tricycles, testosterone, sarkomycin, biotin, etc., have been described earlier [17].

Isoxazolines exhibit interesting and diverse biological properties and represent a unique class of pharmacophores that is present in many therapeutic agents. The brominated isoxazoline alkaloids present in sponges behave as a defense for *T. perversa* [18]. Nucleosides containing the isoxazoline moiety exhibit antiviral activity [19]. The glycoprotein (GP) IIb/IIIa antagonistic properties of some isoxazolines have been extensively investigated [20–22]. There are reports in the recent literature on the FXa inhibitory [23, 24] and apoptotic properties [25] of isoxazolines. Isoxazoline-containing cyclolignan derivatives display potent antiviral, immunosuppressive and cytotoxic activities [26]. Phosphonate-containing isoxazolines enhance the accumulation of indole alkaloids in periwinkle cell cultures [27]. The therapeutic potential of isoxazoline derivatives is further evident from their antimicrobial, anti-

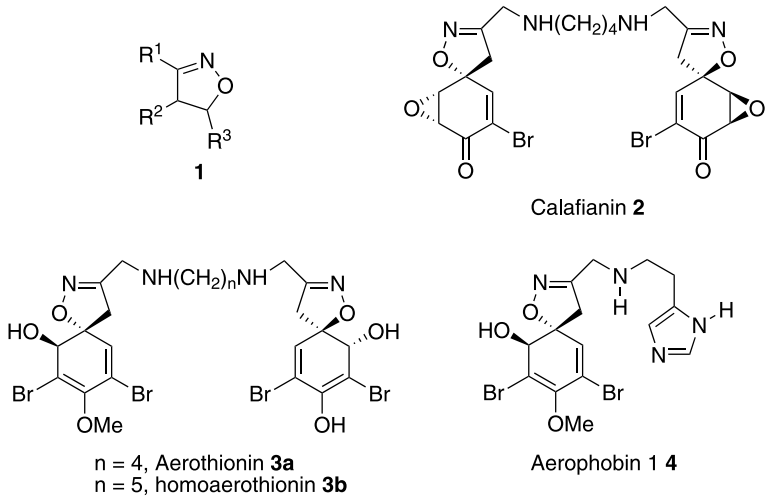


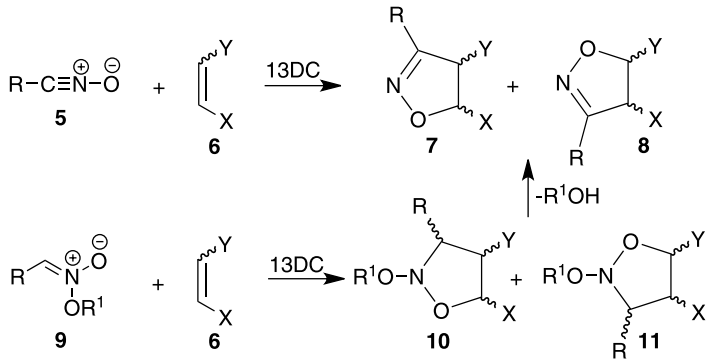
Fig. 1 Bioactive natural products containing isoxazoline moiety

inflammatory, fibrinogen receptor antagonistic, anticancer, antiHIV, caspase inhibitory, and antidepressant properties [28–30].

2
Isoxazolines via 1,3-Dipolar Cycloaddition

1,3-Dipolar cycloaddition (13DC), introduced by Huisgen in the early 1960s [31], is a convenient method for the construction of five-membered heterocycles [32]. Different versions of 13DC including metal-catalyzed [33], asymmetric [34–36], intramolecular [37–39] and solid-phase [40, 41] reactions have been recently reviewed. As for mechanism, both the concerted pathway, in which two new bonds are partially formed in the transition state, although not necessarily to the same extent [42–45], and a non-concerted pathway involving biradical intermediates [46, 47], have been proposed [48]. Earlier, the regiochemistry of 13DC has been rationalized based on the frontier molecular orbital theory (FMO) [49–51] and electrostatic potentials [52]. However, the occasional failure of the original FMO theory in predicting the correct regiochemistry has been attributed to factors such as ambiguity in the nature of the electron demand (inverse vs. normal) [51], repulsive secondary orbital interactions [53], distortions of the alkene in the transition state [54], etc. The regio- and stereoselectivities [55] as well as synthetic applications [56] of 13DC have also received considerable attention in recent years.

13DC of nitrile oxides **5** to olefins **6** is the most general method for the preparation of isoxazolines **7**–**8** (Scheme 1) [5, 57–67]. Nitrones [68–70] and

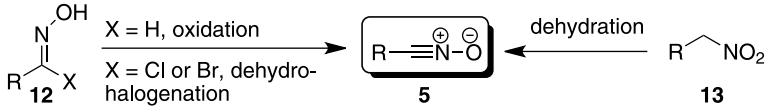


Scheme 1

nitronates, especially silyl nitronates **9** ($R^1 = SiR_3{}^2$) [71–73], which are regarded as synthetic equivalents of nitrile oxides **5**, also react with olefins **6** to afford isoxazolines **7–8** via oxidative elimination of the initial cycloadducts isoxazolidines **10–11** [17, 38, 39]. Other miscellaneous methods reported in recent years include a Pd(0)-catalyzed intramolecular alkylation [74], condensation of hydroxylamine and its derivatives [75–78] etc.

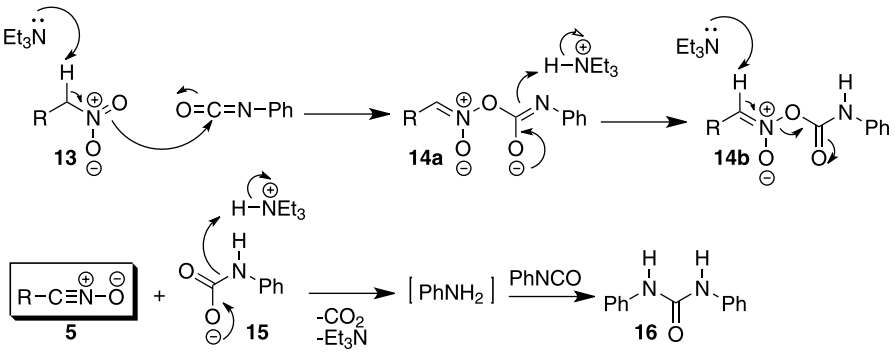
2.1 Generation of Nitrile Oxides and Nitronates

Owing to their tendency to dimerize to furoxans (1,2,5-oxadiazole 2-oxides), nitrile oxides **5** are usually generated in situ, i.e., in the presence of suitable dipolarophiles such as alkenes, alkynes, etc., from stable precursors such as aldoximes **12** (X = H) or from primary nitroalkanes **13** (Scheme 2) [5, 57–67]. Generation of nitrile oxides **5** from aldoximes **12** (X = H) involves either direct oxidation or halogenation of aldoximes **12** (X = H) to hydroximoyl halides **12** (X = Cl or Br) followed by dehydrohalogenation [5, 57–67, 79, 80]. Alternatively, nitrile oxides **5** are conveniently generated via dehydration of primary nitroalkanes **13** [17, 38, 39, 65, 66, 81–95]. This review covers the literature in the last 10–15 years pertaining to the chemistry of isoxazolines synthesized from primary nitroalkanes **13.**



Scheme 2

Since their dehydration with phenylisocyanate and triethylamine was first reported in 1960 by Mukaiyama et al. [81], primary nitroalkanes **13**



Scheme 3

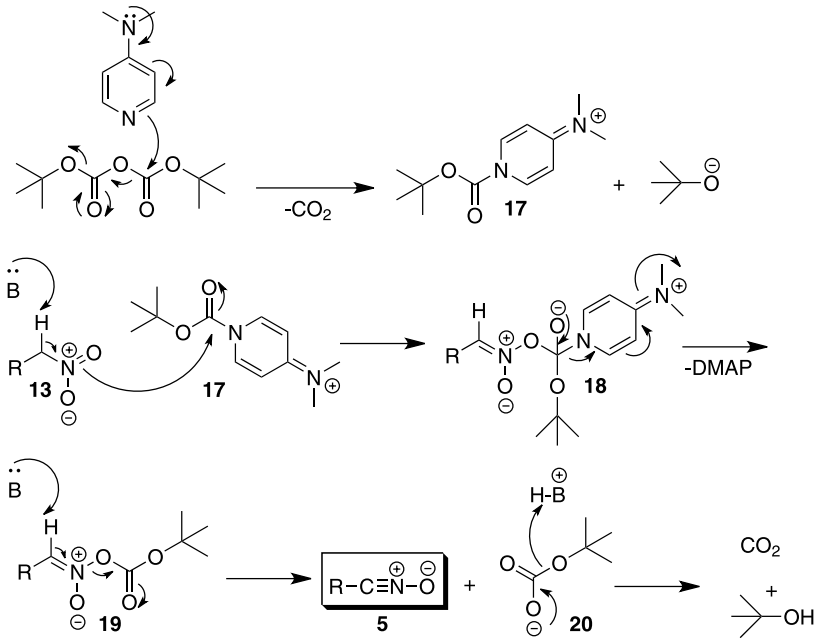
have been a common source of nitrile oxides **5** (see Scheme 3 for a proposed mechanism). A plethora of other reagents such as *p*-toluenesulfonic acid/chloride [82, 83], sodium acetate in acetic anhydride [84, 85], ethyl chloroformate or benzenesulfonyl chloride in the presence of triethylamine [86], etc., have been employed as well for the dehydration of nitroalkanes **13** to nitrile oxides **5**.

Mioskowski and co-workers reported the use of Burgess salt, DAST, oxalyl chloride and phosphorus oxychloride for dehydration of nitroalkanes **13** among which they found DAST to be the best reagent [87]. Recently, a microwave-assisted generation of nitrile oxide **5** under the catalytic influence of 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)/DMAP [88] has been described. However, di-*t*-butyl dicarbonate (Boc_2O)/DMAP, a method reported by Basel and Hassner, allows the dehydration of nitroalkanes **13** under much milder conditions (Scheme 4) [89]. In fact, this has become an efficient method because of the innocuous nature of the side products (*t*-BuOH and CO_2), which simplifies the purification of the ultimately desired isoxazoline product.

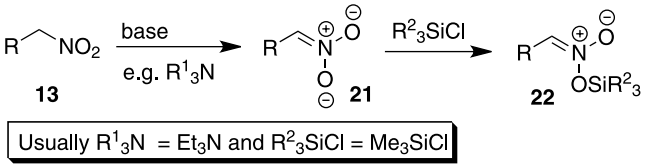
Activated primary nitro compounds, i.e., those bearing an electron withdrawing group (EWG) geminal to the nitro group (i.e., **13**: R = EWG), usually undergo dehydration reaction with acids [90] or under acylation conditions [86] or on thermolysis [91]. Some activated nitro compounds have also been reported to undergo dehydration to nitrile oxides **5** on treatment with Ce(III) ammonium nitrate [92] and thionyl chloride [93].

Machetti and co-workers recently reported the dehydration of several activated nitro compounds such as nitroacetone, benzoylnitromethane, ethyl nitroacetate and phenylsulfonylnitromethane on treatment with tertiary diamines (e.g., DABCO, TMEDA) in the presence of dipolarophiles to afford corresponding isoxazoline derivatives directly [94, 95].

Nitronates **21** are conveniently generated by treating nitroalkanes **13** with a suitable base (Scheme 5). Since the reactivity of nitronate **21** as a dipole is



Scheme 4



Scheme 5

often not satisfactory, it is activated by conversion to its corresponding silyl nitronate **22** [17, 71–73].

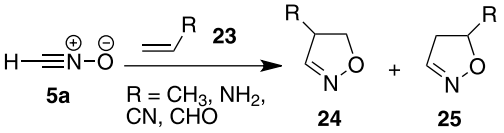
2.2
Nitrile Oxide Cycloadditions Leading to Isoxazolines

Among the dipoles used for the construction of the isoxazoline ring, nitrile oxides have a prominent place in the literature owing to the convenient generation of this intermediate from diverse precursors such as oximes, α-halooximes and nitroalkanes (see Section 2.1). Cycloaddition of nitrile oxides with multiple bonds, especially alkenes, has been extensively investigated in recent years both from the theoretical and synthetic perspectives.

2.2.1 Mechanism and Regio/Stereochemistry

Since the 1960s, the regio- and stereochemistry as well as the overall mechanism of 13DC reaction of nitrile oxides have intrigued organic chemists. As briefly discussed before, these aspects have been addressed from different perspectives adopting various theoretical approaches [42–54]. However, with the advent of high-level ab initio and density functional theoretical (DFT) methods, predictions on the mechanism and selectivities became more reliable.

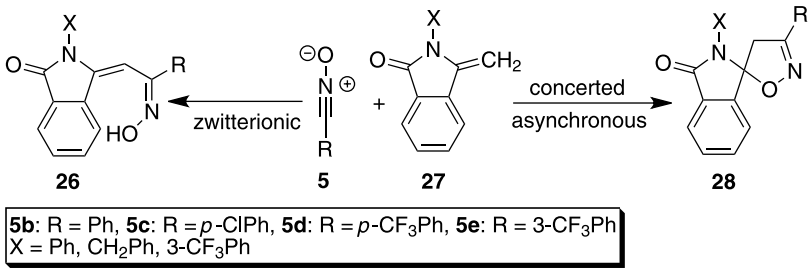
Magnuson and Pranata investigated the electronic effects in the cycloaddition of formonitrile oxide **5a** with substituted ethylenes **23** at RHF and DFT (B3LYP) using 6-31G* basis sets (Scheme 6) [96]. They found the reactions to be asynchronous with early transition states. With electron donating substituents (e.g., CH_3, NH_2) C–C bond is formed to a greater extent than the C–O bond and the substituents R were preferentially directed towards the oxygen end of the dipole affording primarily 5-substituted isoxazolines **25**. However, with electron-withdrawing substituents on the double bond (e.g., CN, CHO) C–O bond is formed to a greater extent and increased preference for the opposite regioisomer **24** is predicted.



Scheme 6

The cycloaddition of ethylene with nitrile oxides and other 1,3-dipoles was studied by Su et al. using DFT and CCSD(T) calculations [97] who found that the activation energy for the 13DC is small and the reaction is exothermic. They also showed that the configuration mixing (CM) model can predict the relative activation energies and reaction enthalpies and concluded that a 1,3-dipole with an electropositive substituent at the terminal position will possess a smaller singlet-triplet splitting that facilitates cycloaddition with a dipolarophile resulting in large exothermicity.

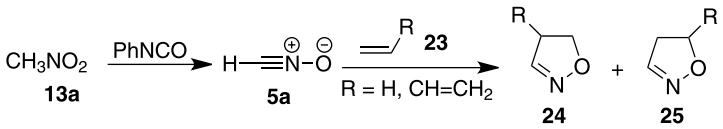
Recently, Domingo et al. investigated the 13DC of electrophilically activated benzonitrile oxide (BNO) **5** with 3-methylenephthalimidine (MPI) **27** using DFT at the B3LYP/6-31G* level (Scheme 7) [98]. Two competing pathways, the 13DC leading to isoxazoline **28** via a concerted but asynchronous transition state and a stepwise one involving a zwitterionic intermediate leading to oxime **26** were proposed. The nucleophilic attack of the methylene carbon of the MPI **27** on the carbon atom of the electrophilically activated BNO **5** was considered as the initiating step in both the reactions.



Scheme 7

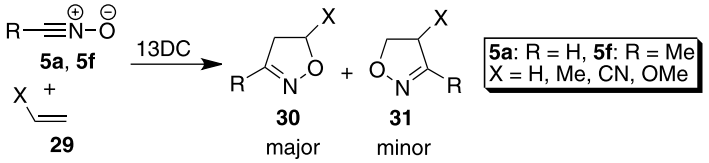
A similar quantum chemical study (MP2 and B3LYP) on the cycloaddition of nitrile oxides with propene under the influence of Lewis acid was performed by Wagner et al., who found little influence of Lewis acids (BH_3, BF_3 etc.) on the outcome of the reaction [99].

According to Schleyer and co-workers, who performed theoretical calculations on the mechanism and regiochemistry of 13DC reactions of formonitrile oxide **5a** with alkenes **23**, the transition states are generated by a concerted supra–supra process and have aromatic character (Scheme 8) [100]. Polar solvents increase the activation barrier for the cycloaddition and electrostatic interaction between atoms and groups favoring the asynchronous and less aromatic transition states. As for regiochemistry, the transition state associated with the formation of 5-isoxazoline **25** was 3.32 kcal mol^{-1} lower in energy than that for 4-isoxazoline **24** in the gas phase at B3LYP/6-31+G* level of theory. This result was reproduced by solvent ($CHCl_3$) model calculations as well (3.32 kcal mol^{-1} in favor of 5-isoxazoline). The authors concluded that the regioselectivity is governed by the more favorable energy of the product **25** rather than by the relative aromaticities of the regioisomeric transition states.



Scheme 8

The regiochemistry of 13DC of nitrile oxides with various dipolarophiles was investigated theoretically at ab initio/DFT level by Rastelli and coworkers (Scheme 9) [101]. Taking formonitrile oxide **5a** as the prototype 1,3-dipole and ethylene with both electron donating (e.g., methyl vinyl ether) and electron-withdrawing (e.g., acrylonitrile) substituents, the authors demonstrated that the 5-isoxazolines **30** are the predominant or exclusive adducts. Therefore, the experimental results are reproducible by calculations if electron correlation is introduced either via Moeller–Plesset perturbation tech-



Scheme 9

nique or via DFT (B3LYP), especially when solvent effects are included. Their studies also explain why FMO theory with uncorrelated Hartree–Fock wave functions is unable to predict the correct regiochemistry. The energy barrier calculated for the reaction between formonitrile oxide and ethylene for the concerted pathway has been estimated to be 11.4 kcal mol^{-1} at the B3LYP/6-31G* level.

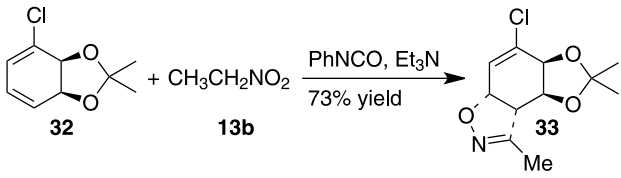
2.2.2
Synthesis of Isoxazolines

Inter- and intramolecular 13DC reactions of nitrile oxides have emerged as a strategy of choice for the construction of isoxazoline rings that are functionalized and fused to other carbo- and heterocycles and hence to polyfunctional compounds.

2.2.2.1
Intermolecular Nitrile Oxide Cycloadditions

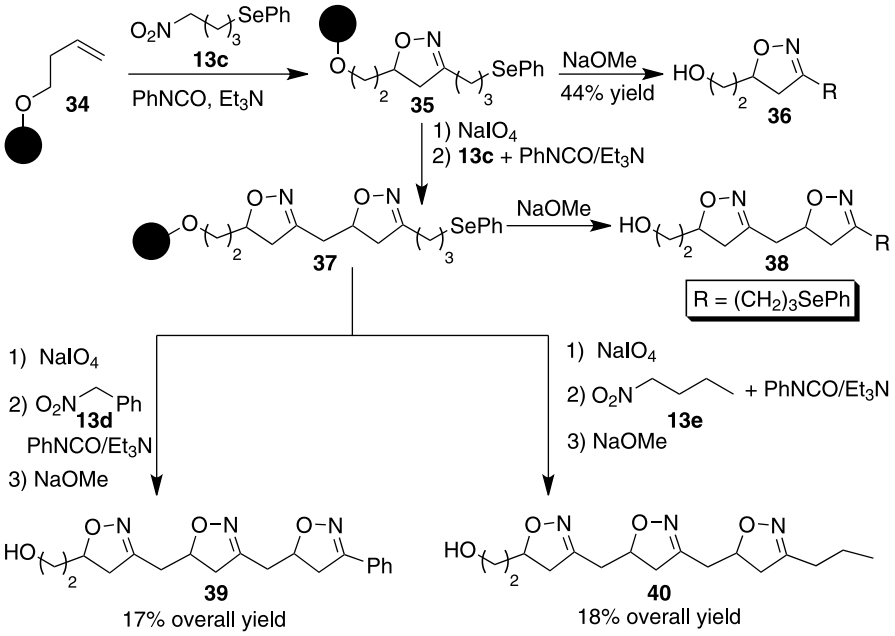
The intermolecular version of nitrile oxide cycloaddition offers the advantages of obtaining isoxazoline rings with a multitude of functionalities from readily available starting materials. However, the cycloadditions are inherently less selective as compared to their intramolecular counterparts and, therefore, formation of mixture of regio/stereoisomers is often encountered.

Hudlicky and McKibben reported the cycloaddition of 1-chloro-5,6-*cis*-isopropylidenedioxycyclohexa-1,3-diene **32** with the nitrile oxide generated from nitroethane **13b** under Mukaiyama conditions (Scheme 10) [102]. The bicyclic product **33** formed stereoselectively and regioselectively in 73% yield was projected to be a potential precursor to antibiotics and natural products.



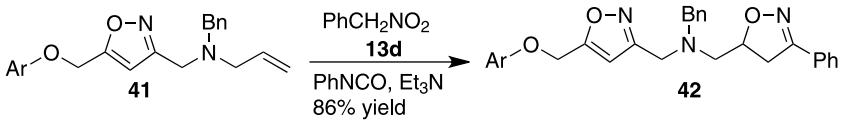
Scheme 10

Kurth and co-workers prepared libraries of polyisoxazolines **39,40** by solid-phase combinatorial synthesis utilizing polymer-bound olefin **34**, nitroselenoethers **13c** and nitroalkanes **13d,e** (Scheme 11) [103]. An iterative application of nitrile oxide 1,3-dipolar cycloaddition followed by selenide oxidation/elimination steps was employed to afford polymer bound tri-isoxazolines which could be liberated from the resin via trans-esterification to afford **39,40.**



Scheme 11

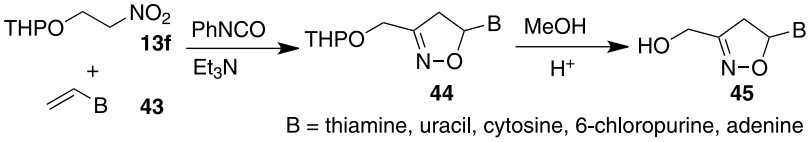
Isoxazole-isoxazoline polyheterocyclic systems have been synthesized for applications as ionophores using resin bound alkenes/alkynes as dipolarophiles. For instance, the isoxazole possessing an alkene moiety **41** was reacted with a nitrile oxide, generated from nitroalkane **13d** under Mukaiyama conditions, to afford isoxazoline **42** in high yield (Scheme 12) [104].



Scheme 12

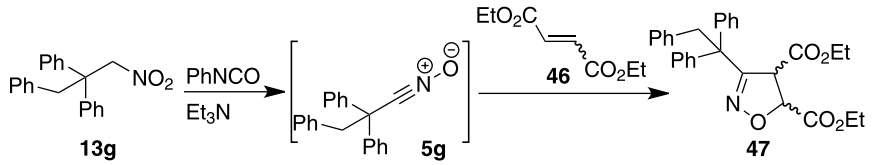
Zhao and co-workers reported a regioselective cycloaddition of nitrile oxide generated from nitroalkane **13f** with *N*-vinyl bases **43** to generate nucle-

oside analogs of isoxazolines **45** (Scheme 13) [105–107]. The bases (B) include thiamine, uracil, cytosine, 6-chloropurine and adenine.



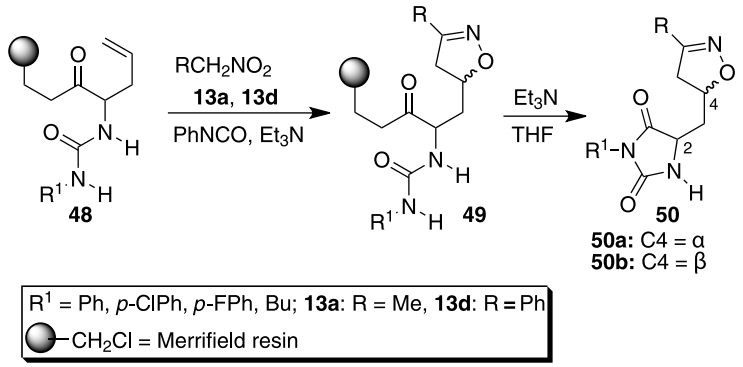
Scheme 13

When nitrile oxide **5g**, generated in situ from nitroalkane **13g**, was reacted with diethyl fumarate and diethyl maleate **46**, stereospecific cycloaddition took place to afford the adducts **47** in 35% and 60% yield, respectively (Scheme 14) [108]. However, when presynthesized nitrile oxide **5g** was used, the yields improved to 98% and 93%, respectively.



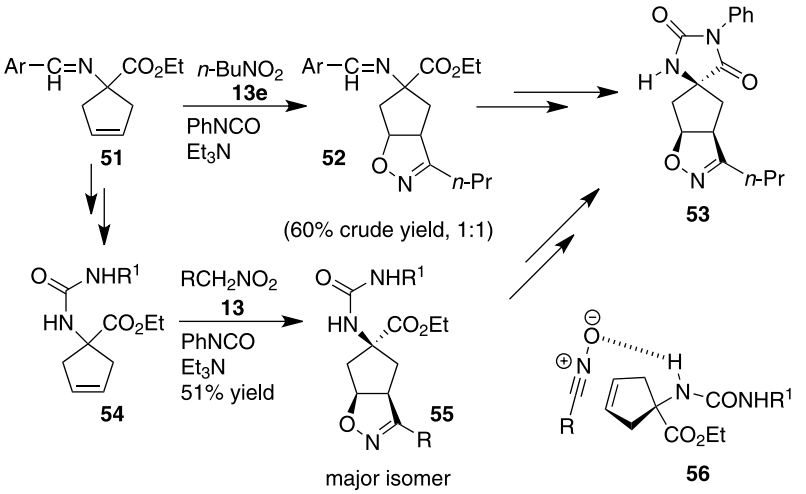
Scheme 14

As part of their solid- and solution-phase synthesis of novel hydantoin-isoxazoline containing heterocycles, Kurth and co-workers reacted solid supported urea intermediates **48**, possessing an alkene moiety with nitrile oxides derived from nitroalkanes **13a** and **13d** to afford isoxazolines **49** as a 1:1 mixture of diastereomers (Scheme 15) [109]. The urea functionality in **49** was then cyclized to obtain hydantoin **50**.



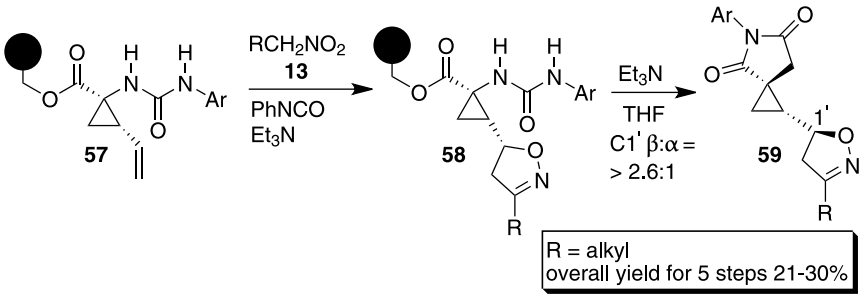
Scheme 15

The same group reported the synthesis of hydantoin linked to cyclopentaisoxazoline starting from activated/protected derivative of glycine and *cis*-1,4-dichloro-2-butene [110]. When the cyclopentene carboxylate **51** was reacted with the nitrile oxide generated from nitrobutane **13e** under Mukaiyama conditions, the labile cycloadduct **52** was isolated as a 1:1 mixture of diastereomers which was subsequently converted to hydantoin **53** (Scheme 16). On the other hand, when the Schiff's base **51** was first converted to urea **54** and then subjected to nitrile oxide cycloaddition, there was considerable diastereoselection which the authors attributed to a hydrogen bonding between N–H of the urea moiety and the oxygen of nitrile oxide as shown in **56**.



Scheme 16

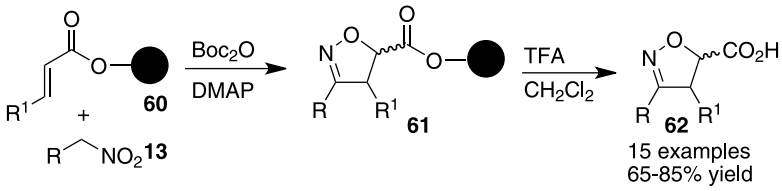
The same authors also reported the solid-phase version of the above hydrogen-bond-directed cycloaddition in which complete diastereoselectivity was observed during the nitrile oxide cycloaddition step [111]. However,



Scheme 17

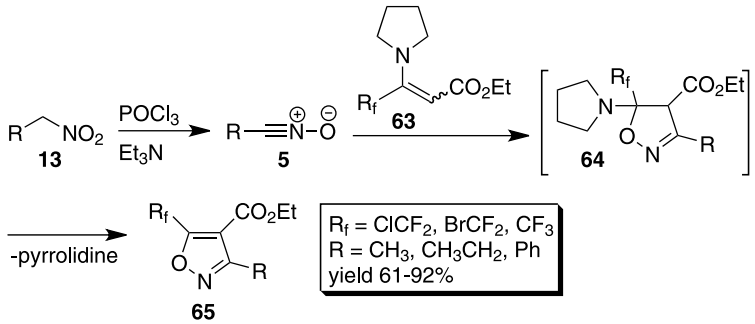
the diastereoselectivity in the solid-phase synthesis of cyclopropenoid isoxazoloimidazolidinedione **59** was low (Scheme 17).

Chandrasekhar et al. synthesized a library of 15 isoxazolines **61** from nitroalkanes **13** and polymer-bound electron-deficient olefins **60** under Hassner conditions (Boc_2O, DMAP) (Scheme 18) [112]. The isoxazoline carboxylic acids **62** were then liberated from the resin on treatment with TFA in CH_2Cl_2 (1:4).



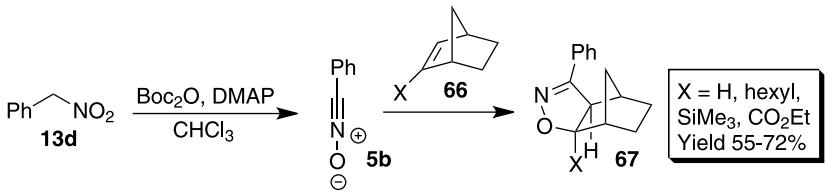
Scheme 18

Nitrile oxides **5** generated via dehydration of nitroalkanes **13** using $POCl_3/Et_3N$ were reacted with perfluoroalkyl pyrrolidino acrylates **63** to afford isoxazolines **64** which underwent spontaneous elimination of pyrrolidine to deliver isoxazoles **65** in good yield (Scheme 19) [113].



Scheme 19

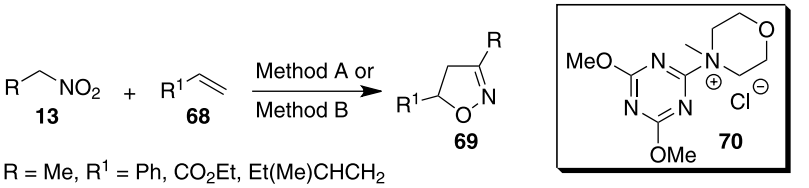
Tam and co-workers investigated cycloaddition of nitrile oxide **5b** with unsymmetrically substituted norbornenes **66** (Scheme 20) [114]. The nitrile



Scheme 20

oxide **5b** generated from nitroalkane **13d** by the Boc_2O/DMAP method provided single regio and stereoisomers of tricyclic isoxazolines **67**. The approach of the nitrile oxide **5b** from the exo face of the bicyclic framework **66** and bonding between the negative end of the dipole **5b** and the carbon bearing the substituent in **66** led to the observed stereo- and regioselectivity.

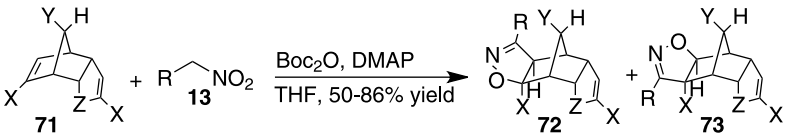
Giacomelli et al. have generated nitrile oxides from nitroalkanes **13** using DMTMM (4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride) **70** as the dehydrating agent in the presence of DMAP in acetonitrile and reacted them with alkenes **68** to afford isoxazolines **69** (Scheme 21) [88]. The authors found microwave irradiation conditions to be superior to the conventional room temperature method.



R = Me, R^1 = Ph, CO_2Et, Et(Me)$CHCH_2$
Method A: DMTMM, DMAP, CH_3CN, 20 °C, 6-12 h, 45-87% conv
Method B: DMTMM, DMAP, CH_3CN, MWI, 3 min, 99% conv

Scheme 21

Namboothiri and co-workers investigated nitrile oxide cycloadditions to dicyclopentadiene **71a** and its derivatives **71b–d** (Scheme 22) [115]. The authors reported generation of nitrile oxides from oximes as well, but the selectivities were independent of the method of generation of nitrile oxides. The influence of remote substituents on the regioselectivity has also been investigated using 8-hydroxy and 1-keto derivatives **71c** and **71d**, respectively, of dicyclopentadiene. The chemo-, stereo- and regioselectivities observed in these cycloadditions were supported by high level ab initio/DFT calculations.

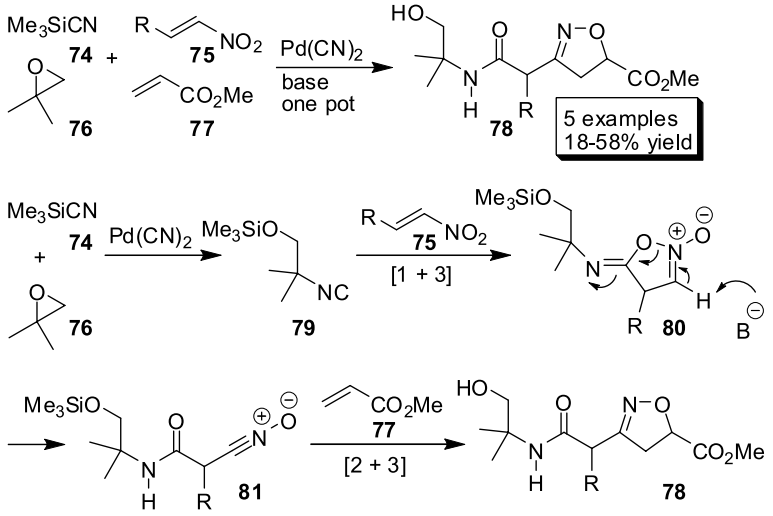


71a: X = Y = H, Z = CH_2; R = Me or Ph; **72a**:**73a** = ~55:45
71b: X = CO_2Me, Y = H, Z = CH_2; R = Me or Ph; **72b**:**73b** = >99:1
71c: X = H, Y = OH, Z = CH_2; R = Ph, **72c**:**73c** = ~55:45
71d: X = Y = H, Z = CO; R = Ph, **72d**:**73d** = 34:66

Scheme 22

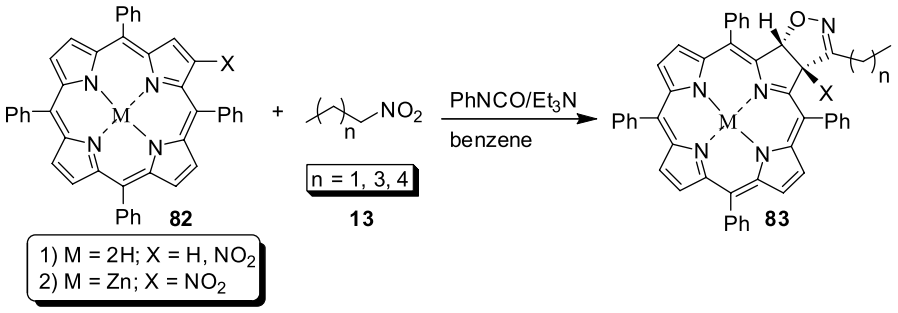
Parsons and co-workers reported a multi-component reaction (**74** + **75** + **76** + **77**) involving sequential [1+3] and [2+3] cycloadditions for the synthesis

of fused and functionalized isoxazolines (Scheme 23) [116]. The original intramolecular reaction reported in 1989 by the same group was elaborated to include intermolecular versions and in situ generation of isocyanides **79**. The sequence involves generation of isocyanide **79** via ring opening of epoxide **76** with trimethylsilyl cyanide **74** followed by [1+3] reaction of the isocyanide **79** with nitroalkene **75** to form *N*-(isoxazolylidene)alkylamines **80**. Fragmentation of the ring to form nitrile oxide **81** and the latter's intermolecular 13DC with electron deficient dienophiles, e.g., **77**, produces isoxazolines **78**.



Scheme 23

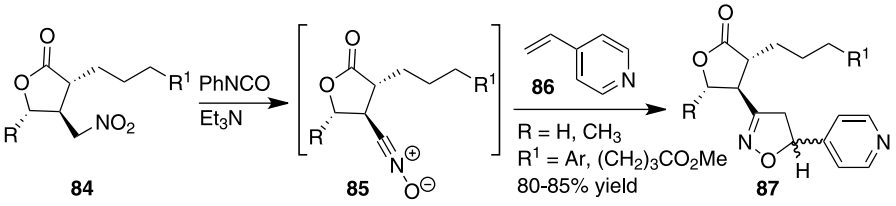
meso-Tetraphenylporphyrin **82** and its β-nitro zinc complex derivative react at higher temperature with in situ generated unstable alkyl nitrile oxides from the corresponding nitroalkanes **13** affording isoxazoline-fused chlorins



Scheme 24

83 (Scheme 24) [117, 118]. The products obtained are attractive intermediates for further functionalization of porphyrins and may be of potential use as sensitizers in photodynamic therapy.

Pashkovskii and co-workers synthesized heterocyclic analogs of prostaglandin or 10-oxa-prostanoids with the isoxazoline moiety in the α- or ω-side chain (see **87**) starting from butenolide **84** containing the nitromethyl moiety (Scheme 25) [119].

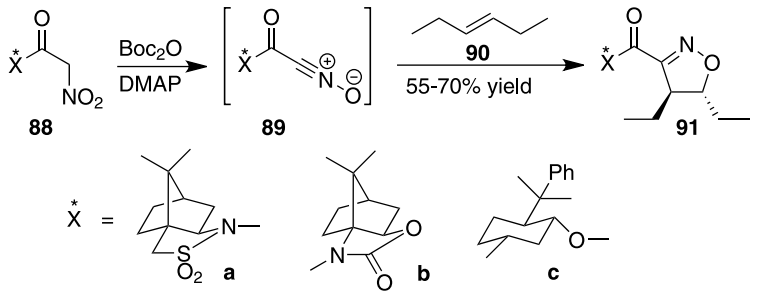


Scheme 25

Asymmetric Intermolecular Nitrile Oxide Cycloadditions

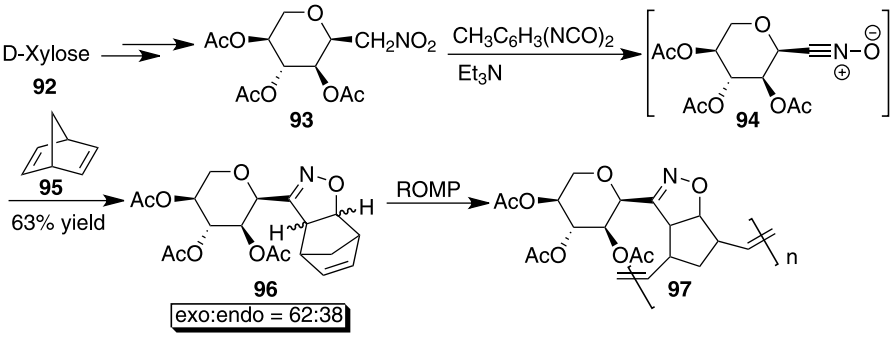
Both the chiron and the auxiliary approaches have been adopted for developing the asymmetric versions of intermolecular 13DC of nitrile oxides generated from nitroalkanes as described below. To our knowledge, the corresponding catalytic approach remains obscure.

Nitroalkanes bearing a chiral unit **88** were employed for generation of enantiopure nitrile oxides **89** (Scheme 26) [120]. These nitrile oxides reacted with (*E*)-hexene **90** to afford 2-isoxazolines **91** in moderate yields and low stereoselectivities (de for trans 10–15%). Similar results were obtained when oximes were used as substrates for nitrile oxide generation.



Scheme 26

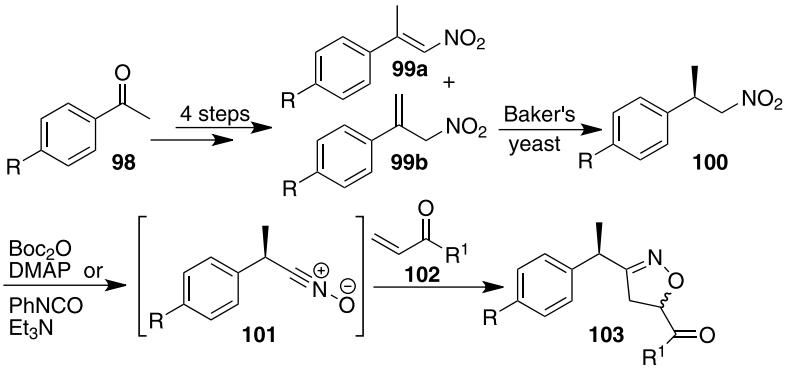
Sugar-derived nitrile oxides **94**, generated from corresponding nitroalkanes **93** using tolylene diisocyanate and triethylamine, were reacted with norbornadiene **95** to afford isoxazolino norbornene derivatives **96** containing sugar residues (Scheme 27) [121]. These were subsequently subjected to



Scheme 27

living ring opening metathesis polymerization (ROMP) to afford new glycopolymers **97**.

Zagozda and Plenkiewicz reported a synthesis of enantiopure isoxazolines **103** via 13DC of optically active nitrile oxides **101** with MVK and acrylate **102** (Scheme 28) [122]. The nitrile oxide precursor **100** was prepared from nitroalkenes **99a,b** by Baker's yeast promoted reduction. While the Mukaiyama procedure (PhNCO, Et_3N) was satisfactory for the generation of nitrile oxide **101** in some cases, the Hassner method (Boc_2O, DMAP) provided better results in other cases. Although yields were satisfactory (35–55%), stereoselectivity remained low (≤65:35).

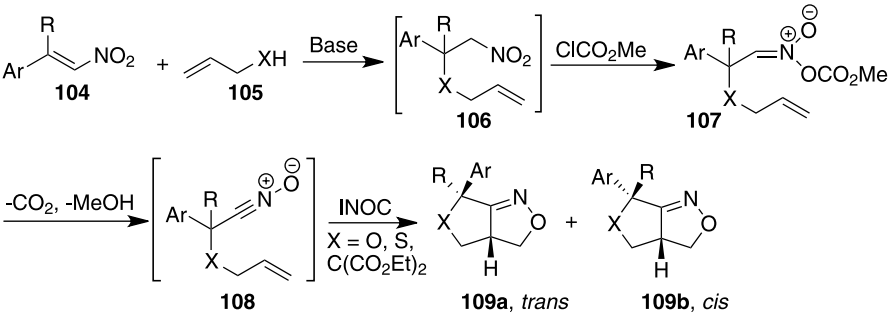


Scheme 28

2.2.2.2 Intramolecular Nitrile Oxide Cycloadditions

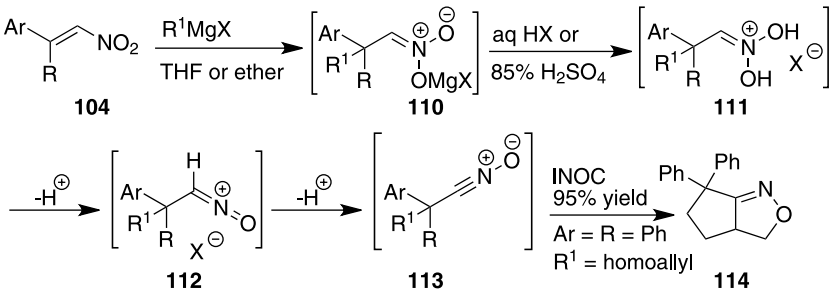
The possibility of formation of two or more rings in a single step with high regio- and stereoselectivity renders the intramolecular version of nitrile oxide cycloaddition particularly attractive. Such reactions are also favored by entropy and offer a convenient entry into polycyclic compounds and natural products. Among the first studies of stereoselective and regioselective intramolecular nitrile oxide-olefin cycloadditions (INOC) leading to the synthesis of bicyclic compounds of type **109** and others, containing either N, C, O or S, are those by Hassner et al. [123–129], some of which will be discussed in a later section (see Sect. 2.4).

Yao and co-workers simplified a known two-step methodology for the synthesis of five-membered cyclic ethers and thioethers (X = O, S) into a one-pot method (Scheme 29) [130]. The products **106** arising from conjugate addition of O and S centered nucleophiles possessing an unsaturated tether to nitroalkenes **104** were not isolated, but treated with methyl chloroformate to generate nitrile oxide **108** via alkoxycarbonyl nitronate intermediate **107**. The in situ generated nitrile oxide **108** or the alkoxycarbonyl nitronate **107** as such undergoes intramolecular 1,3-dipolar cycloaddition to afford isoxazolines **109** fused to five-membered cyclic ethers and thioethers in good yield and selectivity in favor of trans isomer **109a**. The same group later extended the methodology to carbocycles by using diethyl allyl malonate **105** (X = $C(CO_2Et)_2$) as the Michael donor and isolated the carbocycles **109** (X = $C(CO_2Et)_2$) in 51–95% yield [131].

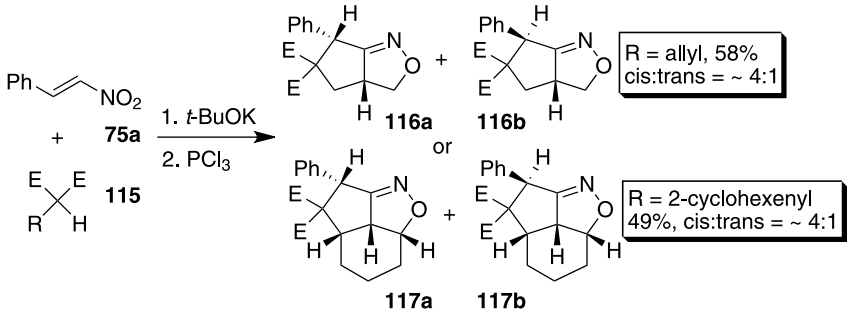


Scheme 29

Yao et al. also reported the synthesis of isoxazoline **114** via conjugate addition of allyl Grignard reagent to nitroalkene **104** and intramolecular 13DC of the in situ generated nitrile oxide **113** (Scheme 30) [132]. According to their proposed mechanism, the magnesium nitronate **110** gets transformed to nitrile oxide **113** upon treatment with aqueous acid.



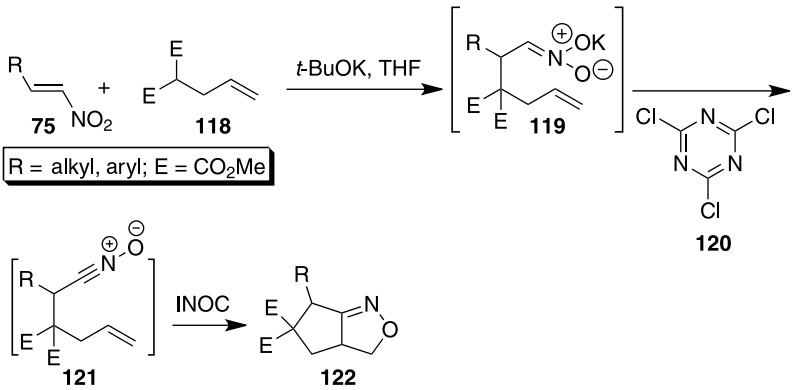
Scheme 30



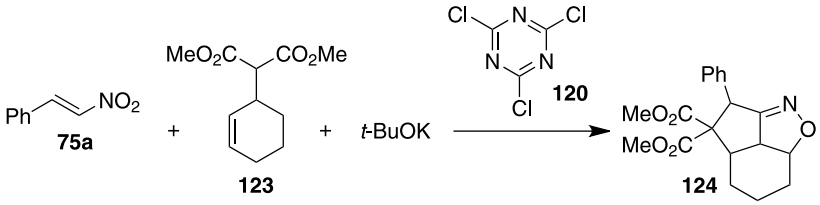
Scheme 31

A similar mechanism was proposed by Yao for the PCl_3-mediated transformation of potassium nitronate to isoxazolines **116** and **117** (Scheme 31) [133].

Yao and co-workers recently used nitroalkenes **75** for the in situ generation of nitrile oxides **121** via nitronates **119** under cyanuric chloride **120**-mediated conditions and synthesized several bicyclic isoxazolines **122** via intramolecular nitrile oxide cycloaddition (Scheme 32) [134].



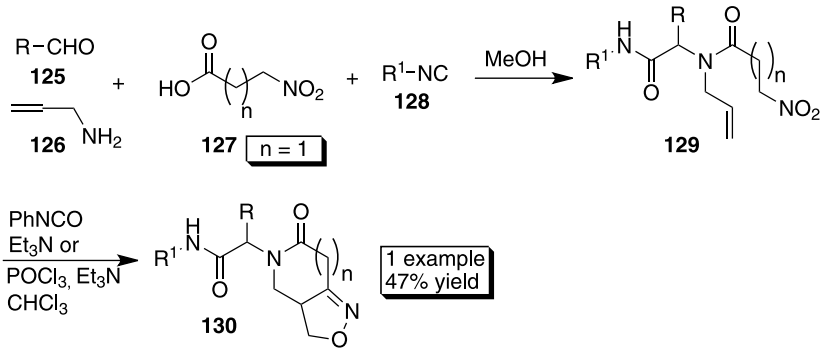
Scheme 32



Scheme 33

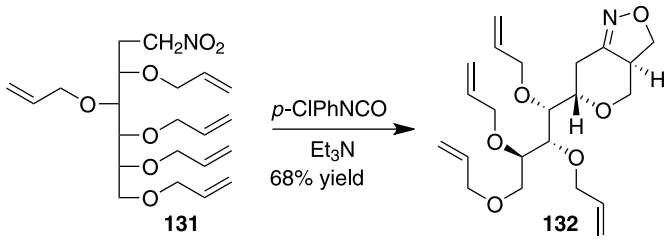
The same strategy was applied efficiently for the synthesis of tricyclic isoxazoline **124** as well (Scheme 33) [134].

Zanze and co-workers recently reported an Ugi reaction followed by intramolecular nitrile oxide cycloaddition for the synthesis of novel isoxazolines **130** (Scheme 34) [135]. The substrates required for INOC were synthesized by a multicomponent Ugi reaction utilizing aldehyde **125**, allyl amine **126**, isocyanide **128** and β-nitro carboxylic acids **127**.



Scheme 34

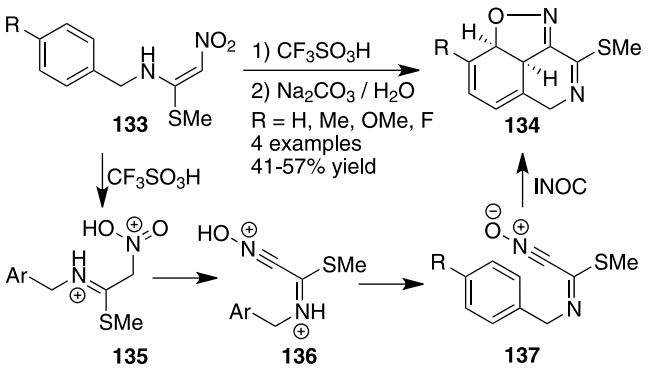
Bhattacharjya and co-workers reported the synthesis of chiral cyclic ether fused isoxazolines via INOC of allyl glucose derivatives [136]. The pentaallyl nitroalkane **131** when subjected to nitrile oxide generation under Mukaiyama



Scheme 35

conditions provided exclusively the pyran fused isoxazoline **132** as a single stereoisomer in 68% yield (Scheme 35).

Coustard and co-workers recently reported an unusual intramolecular nitrile oxide cycloaddition (INOC) that occurs on a single phenyl ring with the full loss of aromaticity of the molecule providing dihydro diazaacenaphthylenes **134** (Scheme 36) [137]. The proposed mechanism involves double protonation of nitroalkene **133** to form the transient dication **135,** which gets converted to hydroxynitrilium ion **136** which is stable at low temperature and characterized by NMR spectroscopy. Quenching of **136** with water generates the reactive nitrile oxide **137** which undergoes INOC reaction with the π-system of the aromatic ring to provide dihydrodiazaacenaphthylene **134.**



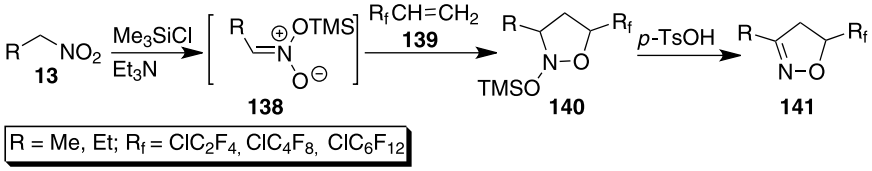
Scheme 36

2.3
Nitronate Cycloadditions Leading to Isoxazolines

Nitronates, particularly silyl nitronates, are often superior to nitrile oxides in their 13DC with olefins in terms of their ease of generation from nitroalkanes, stability, and the observed selectivity during cycloaddition. Cycloaddition of alkyl or silyl nitronates with olefins generates *N*-alkoxy- or *N*-silyloxy-substituted isoxazolidines which then undergo spontaneous or acid catalyzed elimination of alcohol (or silanol) to produce isoxazolines (see Scheme 1, Sect. 2).

2.3.1
Isoxazolines via Silyl Nitronate Cycloaddition

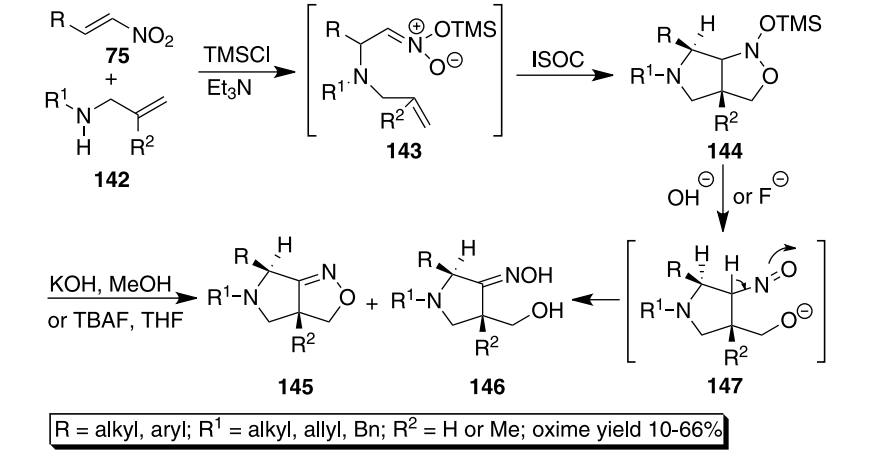
Chen and Hu reported the synthesis of polyfluorinated isoxazolines **141** via 13DC of nitronates or silyl nitronates **138** with polyfluoroalkylethenes **139**



Scheme 37

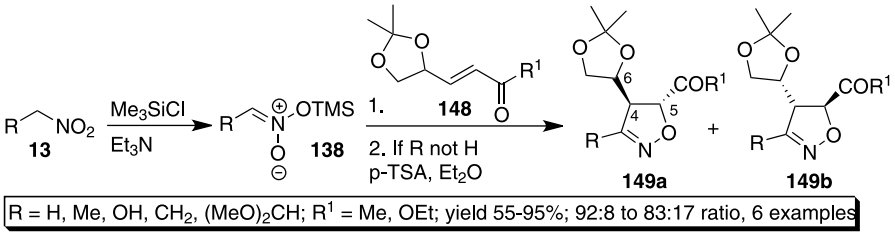
(Scheme 37) [138]. Silyl nitronates **138** generated in situ by the reaction of nitroalkanes **13** with chlorotrimethylsilane provided lesser yields of the products as compared to the yields obtained with the pre-synthesized silyl nitronates **138.**

Gottlieb and Hassner reported a one-pot reaction for the synthesis of highly functionalized pyrrolidines **145** starting from Michael addition of secondary allyl amine **142** to nitroalkenes **75** (Scheme 38) [139]. The resulting nitronate is trapped as silyl nitronate **143,** which undergoes a facile ISOC reaction leading to *N*-silyloxy isoxazolidine **144.** Treatment of the latter with base or fluoride provides a mixture of isoxazoline **145** and oxime **146.** While desilylation-elimination (of water) sequence generates isoxazoline **145,** the sequence involving desilylative ring opening of **144** and tautomerization of the nitroso intermediate **147** furnishes the oxime **146.**



Scheme 38

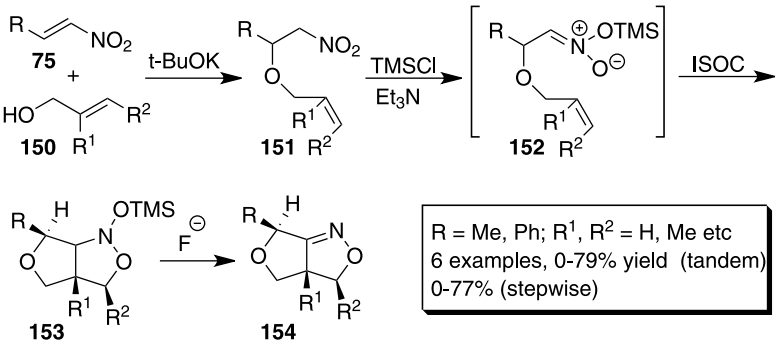
13DC of silyl nitronate **138** with chiral enone and enoate **148** proceeds in good yield and good stereoselectivity to provide enantiopure isoxazolines **149** (Scheme 39) [140]. NMR and X-ray analysis revealed the syn orientation of the hydrogens at C-4 and C-6, a selectivity opposite to that found with ni-



Scheme 39

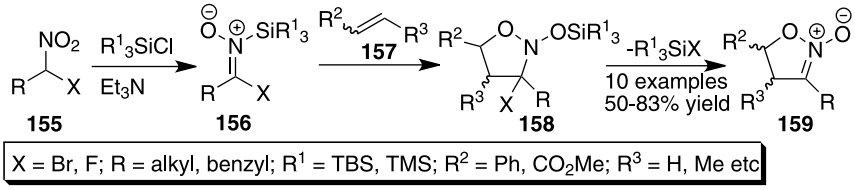
trile oxide cycloaddition, and an anti relationship between substituents at C-4 and C-5.

Hassner et al. reported an oxa-Michael addition of allyl alcohols **150** to nitroalkenes **75** followed by ISOC reaction (Scheme 40) [141]. The ISOC reaction conducted without isolating the intermediate nitroalkane **151** was superior to the stepwise mode in most cases in terms of its one-pot nature and product yield.



Scheme 40

Silyl nitronates **156**, generated from α-halonitro compounds **155**, undergo cycloaddition with a variety of olefins **157** such as styrene, acrylate, norbornene, cyclopentene etc to afford isoxazoline *N*-oxides **159** in good to high

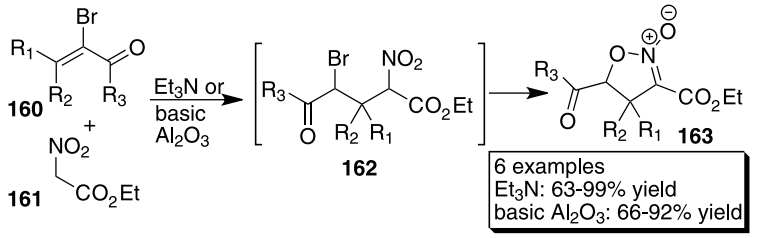


Scheme 41

yields (Scheme 41) [142]. While bromonitro compounds were suitable for terminal alkenes, fluorinated derivatives were employed for internal alkenes.

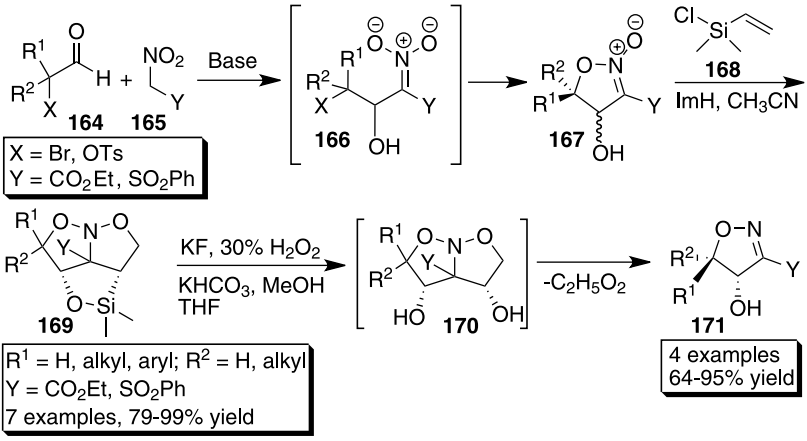
2.3.2
Isoxazolines via Cycloaddition/Cyclization of Alkyl Nitronates

Rosini and co-workers reported the synthesis of 5-acyl-3-(ethoxycarbonyl)-2-isoxazoline-2-oxide **163**, via conjugate addition of ethyl nitroacetate **161** to the α-bromo enones **160** followed by ring closure (Scheme 42) [143]. The reaction was performed under both homogeneous and heterogeneous conditions, but the former was found to be superior in terms of the isolated yield of the product.



Scheme 42

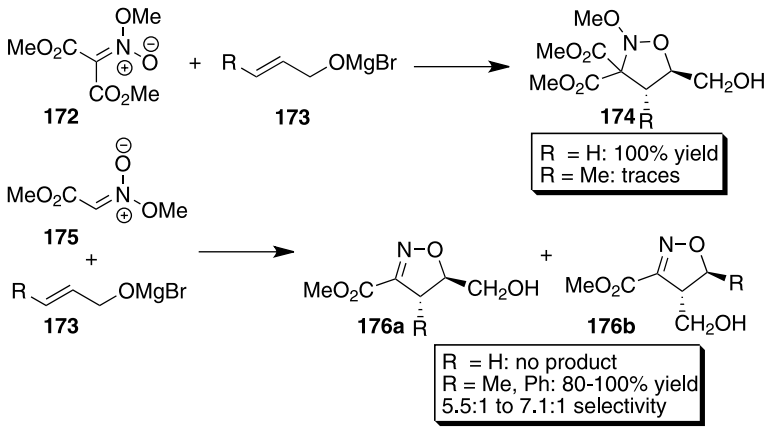
Rosini and co-workers also reported the synthesis of isoxazolines **171** passing through highly functionalized heterocyclic structures bearing nitroso acetal functionality **169–170** all via a multicomponent domino reaction of an activated nitroalkane **165**, an aldehyde bearing a leaving group



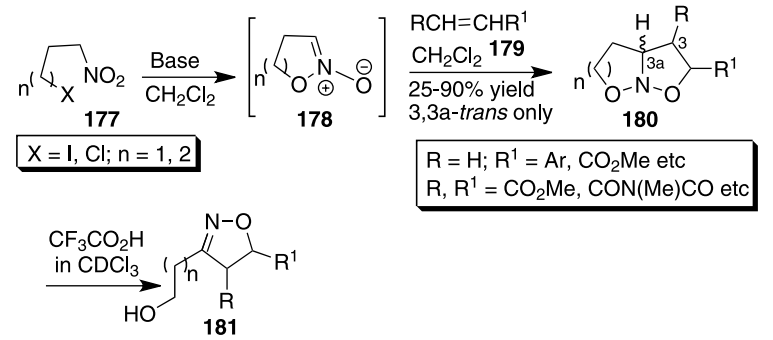
Scheme 43

on the α-carbon **164** and silicon tethered olefin **168** (Scheme 43) [144]. The reaction sequence involves base-promoted nitroaldol reaction between the aldehyde **164** and nitroalkane **165** resulting in the generation of 4-hydroxy-2-isoxazoline-2-oxide **167**. The hydroxy group of **167** then links with the olefinic moiety of **168** and an intramolecular nitronate cycloaddition follows resulting in the tricyclic structure **169**. The tricyclic compounds thus obtained were then transformed into several interesting new heterocycles including some novel isoxazolines **171** and linear aminopolyhydroxylated molecules.

The Kanemasa group utilized the strategy of 13DC of electron deficient activated ester nitronates **172** and **175** arising from dimethyl nitromalonate and methyl nitroacetate, respectively, with the magnesium derivative of allylic alcohols **173** for the synthesis of substituted isoxazolines **174** and **176** (Scheme 44) [145]. The monoester nitronate **175** was originally an *E*:*Z* mixture in 1:1.8 ratio.



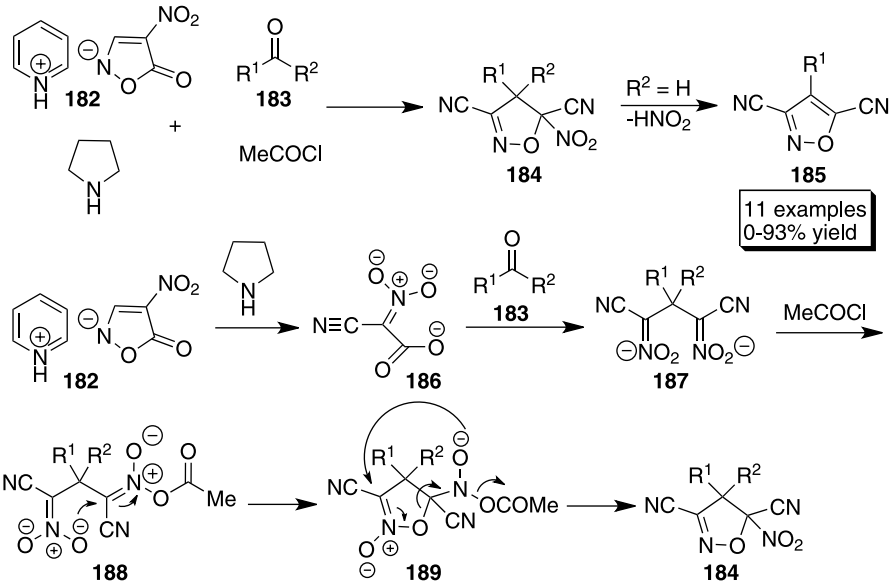
Scheme 44



Scheme 45

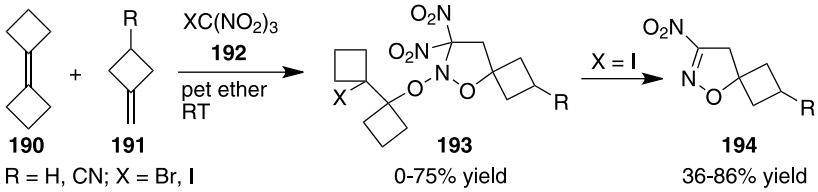
Kanemasa et al. trapped nitronates **178** generated from halo-nitroalkanes **177** with various olefins **179** for the synthesis of isoxazolines **181** (Scheme 45) [146].

Ariga and coworkers reported the synthesis of polyfunctionalized isoxazolines **184** via acylation of dinitronate **187** followed by intramolecular cyclization via a one-pot multicomponent reaction (Scheme 46) [147]. The sequence involves conversion of pyridinium salt of 4-nitroisoxazolin-5(2*H*)-one **182** to cyano-*aci*-nitroacetate **186** which condenses with aldehydes or ketones **183** to provide dinitronates **187**. The intramolecular cyclization of dinitronate **187** is promoted by *O*-acylation which makes one nitronate electrophilic and the other relatively nucleophilic.



Scheme 46

A three-component reaction of halogenotrinitromethanes **192** with alkenes **190** and **191** was carried out for the synthesis of halogen substituted isoxa-



Scheme 47

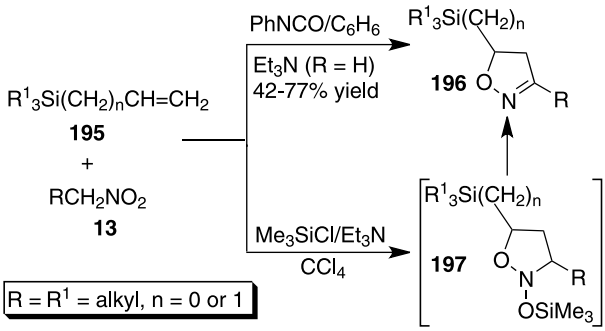
zolidines **193** (Scheme 47) [148]. Among these, iodinated isoxazolidines **193** (X = I) underwent decomposition to afford corresponding isoxazolines **194**.

2.4 Isoxazolines via Nitrile Oxides vs Silyl Nitronates

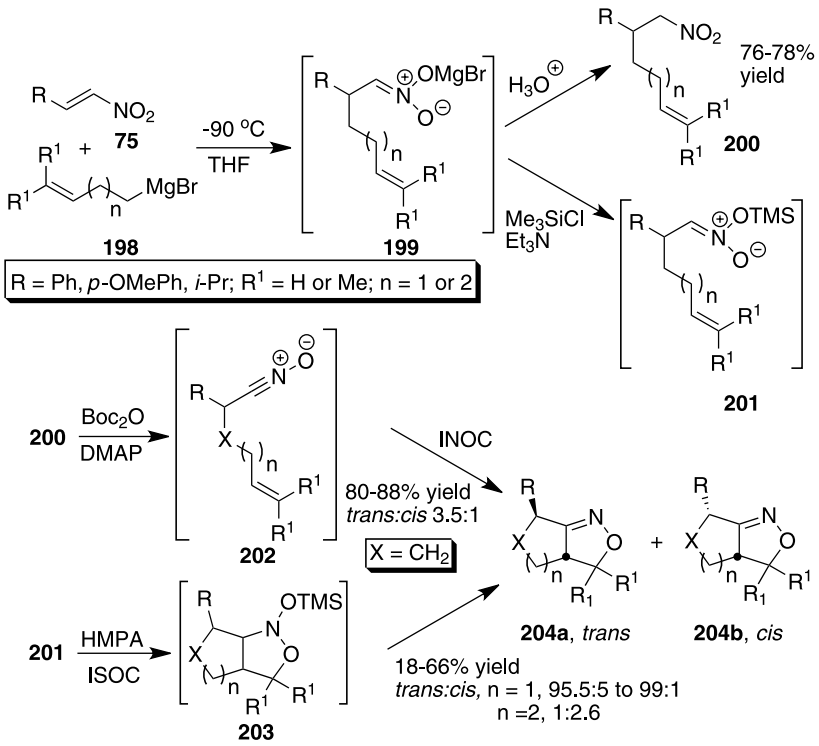
In recent years, many groups reported the synthesis of isoxazolines from nitroalkanes via nitrile oxides as well as via silyl nitronates. However, the seminal studies comparing the intramolecular versions, INOC and ISOC, in the formation of bicyclic regioisomers similar to **204**, (Scheme 49, vide infra) were reported by Hassner [149]. In this communication it was shown that INOC reactions lead to mixtures of stereoisomeric bicyclic isoxazolines (analogs of **204**, X = O, S, or CR_2). On the other hand, a single stereoisomer was obtained in all cases via the ISOC route, regardless of whether the fused ring contained O, S, or only C. Thus, comparison of the two routes suggested that, in general, intramolecular silyl nitronate cycloaddition (ISOC) is superior to the intramolecular nitrile oxide cycloaddition (INOC) in terms of product yield and selectivity.

Many silicon-containing heterocycles possess significant biological activities. In this context, silyl isoxazolines **196** were synthesized by dipolar cycloaddition of nitrile oxides or silyl nitronates with various silicon dipolarophiles **195** such as allyl or vinyl silanes and trialkoxyvinyl silanes (Scheme 48) [150]. Although 5-isoxazoline **196** was the major product, its regioisomer, 4-isoxazoline, was also isolated in small amounts depending upon the nature of substituents on silicon and the method of generation of nitrile oxide (i.e., from nitroalkane or α-halooxime). Similarly, the ratio between 5-isoxazoline **196** and 4-isoxazoline (not shown) was 3.7:1 under the silyl nitronate conditions.

Hassner and coworkers reported a one-pot protocol for the stereoselective synthesis of isoxazolines fused to five- and six-membered carbocycles **204** (Scheme 49) [151]. The method involves conjugate addition of Grignard



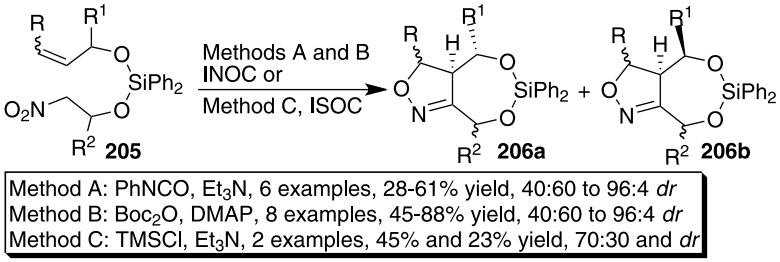
Scheme 48



Scheme 49

reagents possessing an unsaturated tether **198** to nitroalkene **75**, trapping of the nitronate **199** as silyl nitronate **201**, an ISOC reaction and desilylation. While the two-step method via nitrile oxide **202** was less selective (*trans:cis* 3.5:1), the ISOC method provided the isoxazolines **204** in good yield and excellent selectivity (*trans:cis* up to 99:1).

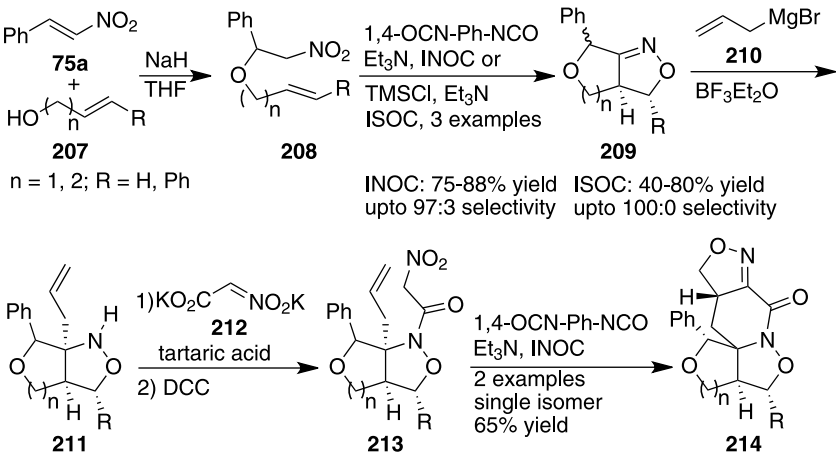
Breau and co-workers reported diastereoselective INOC and ISOC reactions of silaketals **205** derived from allylic alcohols and nitroethanols for the synthesis of 3,4,5-trisubstituted 2-isoxazolines **206** (Scheme 50) [152, 153].



Scheme 50

While the diastereoselectivity was high when the INOC reaction of substrates possessing a chiral center at the allylic position was conducted, the chiral center at the α-position of the nitrile oxide moiety provided the isoxazolines **206** with moderate selectivity [153]. The ISOC provided better selectivity as compared to the INOC at the expense of the product yields.

Kurth and co-workers utilized two 13DC reactions in the same sequence for the synthesis of bis-isoxazolo substituted piperidinone skeleton **214** (Scheme 51) [154]. The reaction sequence involved Michael addition of an unsaturated alkoxide **207** to β-nitrostyrene **75a** followed by INOC or ISOC. The resulting isoxazoline intermediate **209** was subjected to Grignard addition for the generation of the isoxazolidine moiety **211**, which upon DCC-mediated coupling with nitroacetic ester **212** furnished the intermediate **213** bearing both nitroalkane and alkene moiety. This intermediate upon INOC reaction led to the bis-isoxazolo piperidinone nucleus **214**.

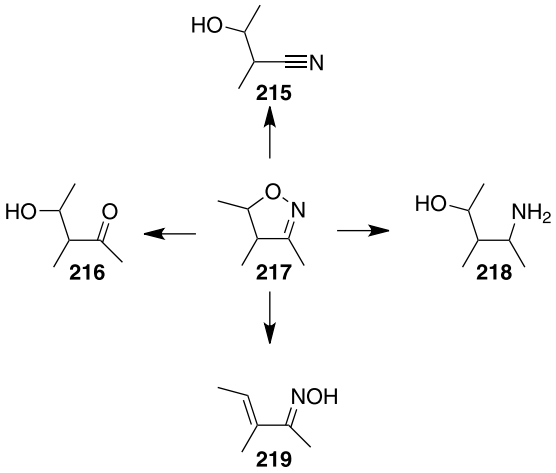


Scheme 51

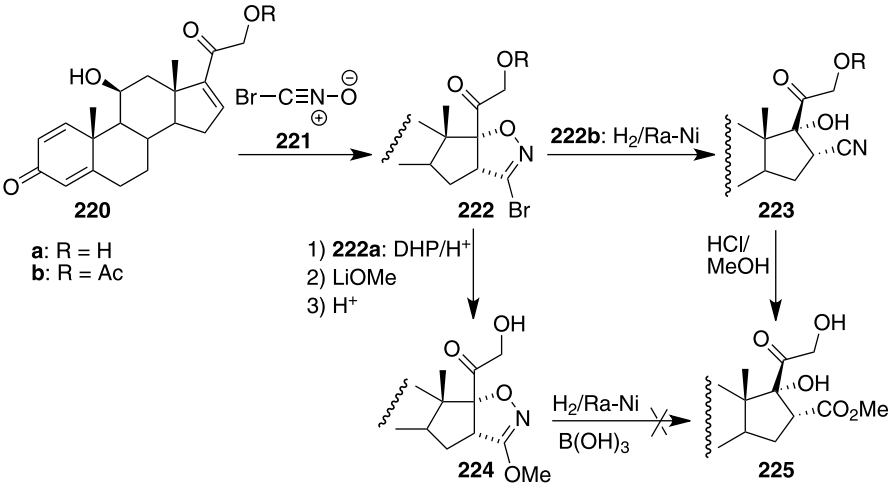
3 Transformations of Isoxazolines

As briefly discussed in the introduction, isoxazolines are excellent precursors to a variety of highly useful synthetic intermediates [3–5]. For instance, N–O bond cleavage of **217** followed by hydrolytic workup provides β-hydroxyketone **216**, and hence provides an alternate route to an aldol product (Scheme 52). The dehydrogenation of intermediate iminoalcohol arising from N–O bond cleavage affords β-hydroxy nitriles **215**. Complete reduction of the isoxazoline ring delivers γ-aminoalcohols **218**. Base-mediated ring opening would provide α,β-unsaturated oximes **219**. All the above hydroxy

compounds can be easily dehydrated or the other functional group can be transformed further to obtain synthetically useful molecules. This section describes transformations of isoxazolines, synthesized via various cycloaddition and cyclization methods, to a variety of synthetic intermediates shown in Scheme 52. However, as far as formation of the isoxazoline moiety is concerned, this discussion is limited, as in the previous sections, primarily to those derived from nitroalkanes.



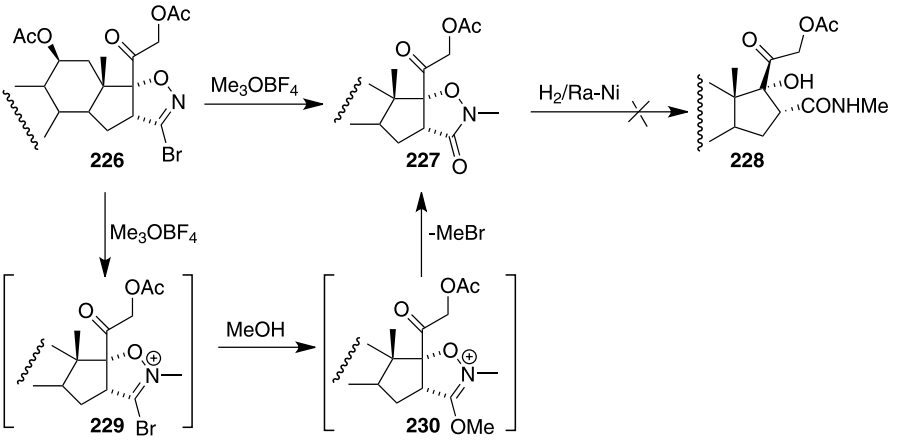
Scheme 52



Scheme 53

Bacher et al. reported the synthesis of a potentially active anti-inflammatory steroid, 16α-carbomethoxyprednisolone **225**, via bromonitrile oxide (**221**) cycloaddition to steroidal enones **220a**,**b** (Scheme 53) [155]. The bromoisoxazoline **222b** was subjected to reductive cleavage and the resulting nitrile **223** was hydrolyzed and esterified to afford **225**. Although direct displacement of bromide in **222** by methoxide was not feasible, the authors succeeded in the above transformation via protection/deprotection of the primary alcohol. However, all attempts to transform methoxyisoxazoline **224** to the ester **225** via reductive cleavage of the N–O bond proved futile.

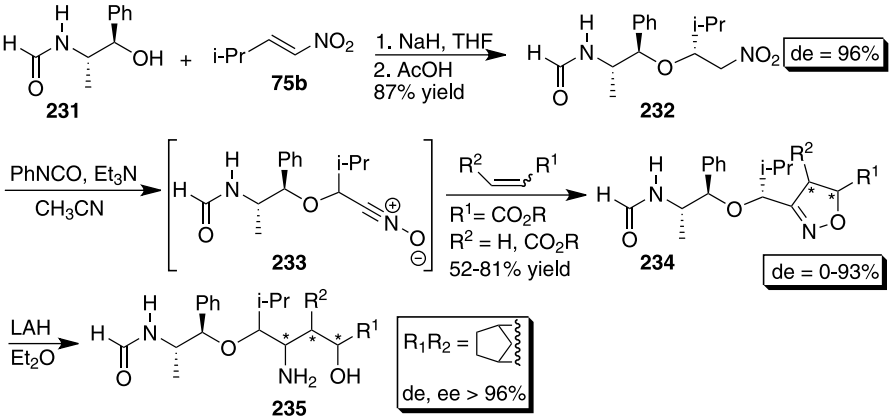
In another approach, the same authors attempted to transform the bromoisoxazoline **226** to the ring opened product **228** via methoxyisoxazolinium salt **230** (Scheme 54) [155]. However, the salt **230** underwent spontaneous elimination of MeBr to afford **227** and the latter was not amenable for N–O bond cleavage.



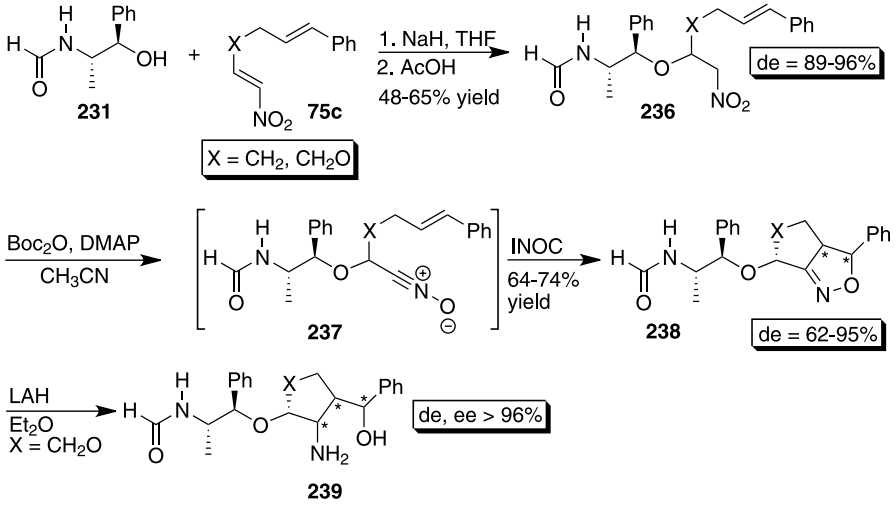
Scheme 54

Enantioselective synthesis of *N*-protected aminodiols **235** and **239** via diastereoselective inter- and intramolecular cycloaddition of optically active nitrile oxides **233** and **237** followed by cleavage of the isoxazolines **234** and **238** has been reported by Enders and co-workers (Schemes 55 and 56) [156]. The nitrile oxides **233** and **237** were generated from nitroalkanes **232** and **236**, respectively, which in turn were obtained by diastereoselective oxa-Michael addition of (1*R*, 2*S*)-(–)-*N*-formylnorephedrine **231** to aliphatic nitroalkenes **75b**,**c**. The $LiAlH_4$-mediated cleavage of isoxazolines **234** and **238** to aminoalcohols **235** and **239**, respectively, proceeded with >96% diastereoselectivity.

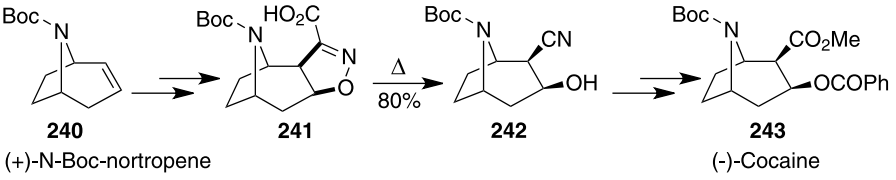
Lin et al. reported the synthesis of (–)-cocaine **243** from a key intermediate, *N*-Boc-nortropene **240**, via nitrile oxide cycloaddition followed by decarboxylation and fragmentation of the isoxazoline ring in **241** under thermal conditions (105–110 °C) (Scheme 57) [157].



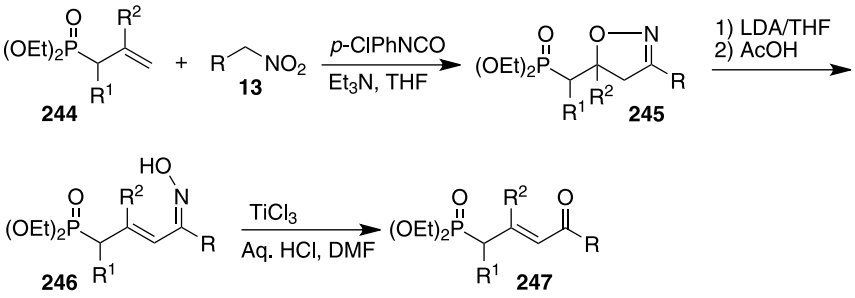
Scheme 55



Scheme 56



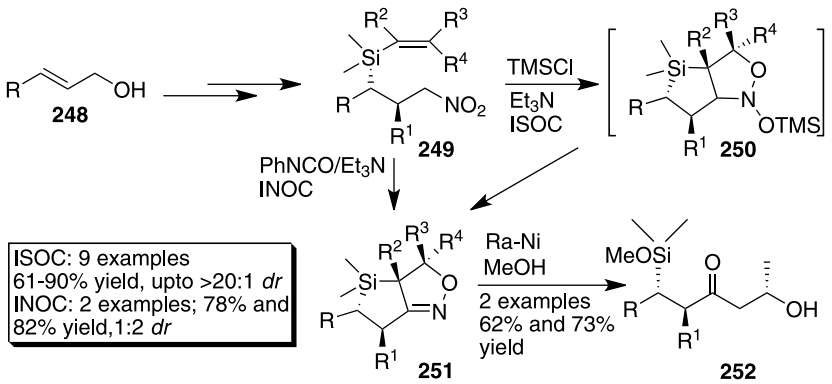
Scheme 57



Scheme 58

Oh and co-workers utilized nitrile oxide cycloaddition chemistry for the preparation of 4-oxo-2-alkenylphosphonates **247** by γ-acylation of allylic phosphonates **244** (Scheme 58) [158, 159]. Regioselective dipolar cycloaddition between nitrile oxides obtained from nitroalkanes **13** and allylic phosphonates **244** serving as dipolarophiles provided phosphonate-containing 2-isoxazolines **245** in good yields. Isoxazolines **245** upon LDA-mediated ring cleavage followed by hydrolysis of the corresponding oximes **246** yielded 4-oxo-2-alkenylphosphonates **247.**

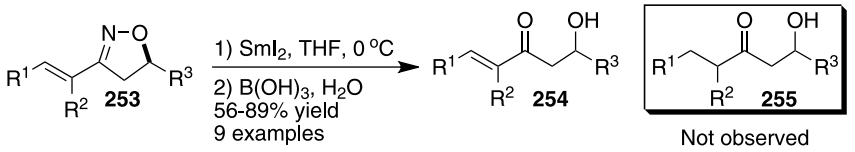
Hoveyda and co-workers employed nitroolefinic silanes **249** possessing a chiral center that bears a silicon substituent for the diastereoselective synthesis of isoxazolines **251** (Scheme 59) [160]. While the silyl nitronate cycloaddition provided the diastereomeric isoxazolines **251** in >20:1 ratio, the nitrile oxide route was much less selective (dr 1:2), in agreement with the findings by Hassner as shown in Scheme 49. The greater selectivity observed in the ISOC reaction was attributed to a possible 1,3-allylic strain in the transition state leading to the minor isomer while no such strain was expected for nitrile oxides that have near-linear geometry. The authors also observed greater



Scheme 59

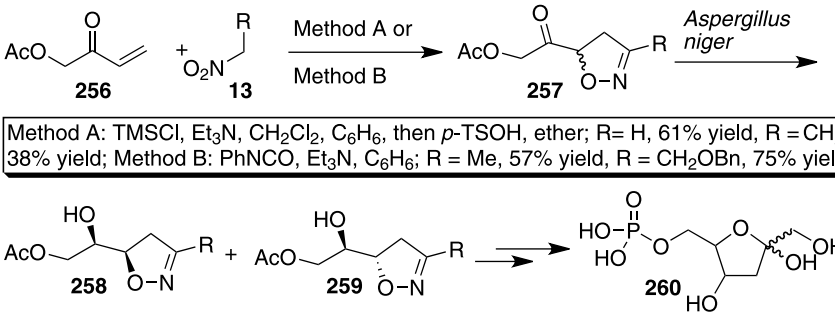
selectivity with more substituted substrates. Subsequent reductive cleavage of the isoxazoline ring in two of the cycloadducts using Raney Ni in methanol proceeded satisfactorily to afford ketoalcohols **252** after hydrolytic workup.

Bode and Carreira recently reported a method for the selective reduction of conjugated isoxazolines **253** to the corresponding unsaturated β-hydroxy ketones **254** (Scheme 60) [161]. This involves selective reduction of N–O bond in **253** by SmI_2 and subsequent hydrolysis of the imine under mild acidic conditions (boric acid). While $Mo(CO)_6$ provided a mixture of the unsaturated hydroxy ketone **254** and its saturated analog **255**, Ra-Ni and SmI_2 in the absence of $B(OH)_3$ provided only the saturated analog **255**.



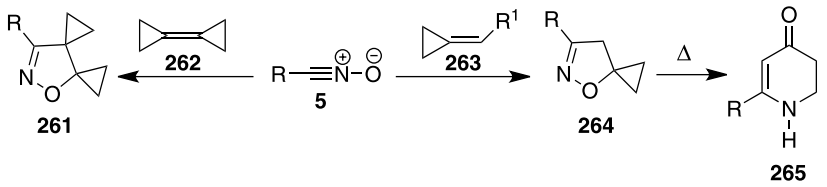
Scheme 60

A series of 5-acylisoxazolines **257** was synthesized by the reaction between acetoxymethyl vinyl ketones **256** and nitroalkanes **13** (Scheme 61) [162]. Both silyl nitronate and nitrile oxide methods were employed in this scheme. The racemic isoxazolines **257** were then biotransformed by *Aspergillus niger* to a 1:1 mixture (syn and anti) of dihydroxyethyl isoxazolines **258** and **259** in good yields and high optical purities. Total synthesis of 3-deoxy-D-fructose-6-phosphate **260** could be achieved in two steps in 64% overall yield from the anti-diol (R = CH_2OBn).



Scheme 61

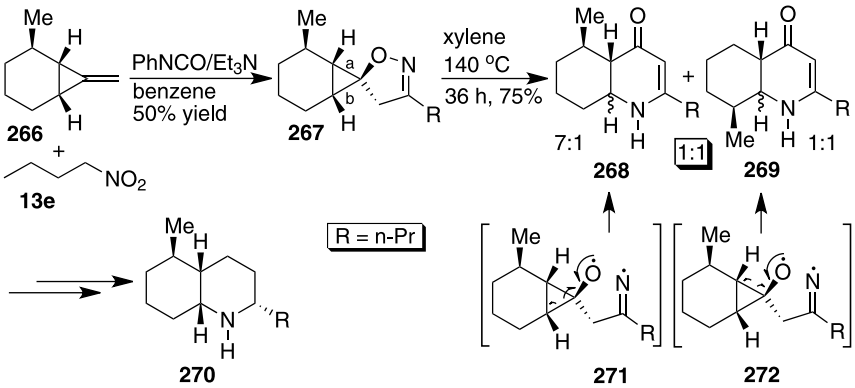
As mentioned in the introduction (Sect. 1), the spiroisoxazoline moiety is found in many natural products [13–16]. Nitrile oxide cycloadditions to methylenecyclopropanes, alkylidenecyclopropanes **263** and bicyclopropylidenes **262** have widely been utilized for the highly regio- and stereoselective synthesis of spiroisoxazolines **264** and **261**, respectively



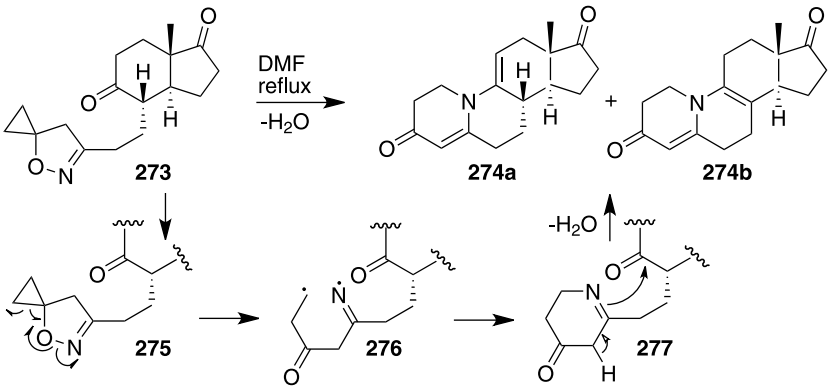
Scheme 62

(Scheme 62) [9, 163]. In the former case, 5-spirocyclopropane **264**, arising from approach of the dipole **5** from the less hindered side of the dipolarophile **263**, was preferentially formed. Spiroisoxazoline was generated in connection with the synthesis of dihydropyrid-4-ones **265** via rearrangement.

The spiroisoxazolines are also important intermediates for the synthesis of various natural and non-natural biologically active molecules such as the amphibian alkaloid (±)-pumiliotoxin C **270** (Scheme 63) [164] and 19-nor-



Scheme 63

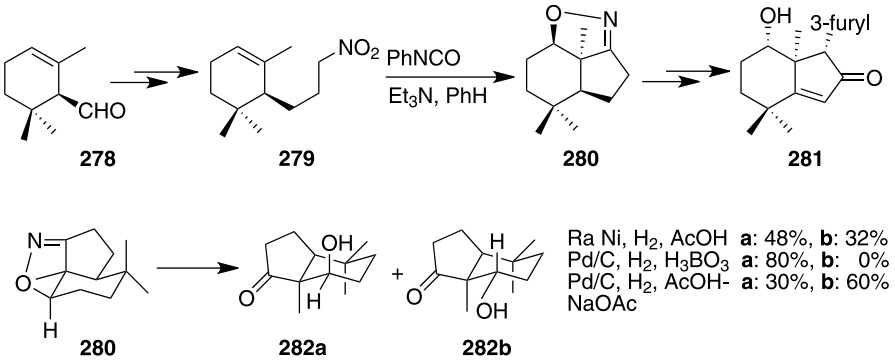


Scheme 64

10-azatestosterones **274a,b** belonging to a novel class of inhibitors of human steroid 5α-reductases (Scheme 64) [165, 166]. The thermolysis of isoxazoline **267** provides a 1:1 mixture of octahydroquinolinones **268** and **269** each one of which is a mixture of diastereomers in 7:1 and 1:1 ratio, respectively (Scheme 63) [164]. This lack of selectivity is attributable to the cyclopropane ring fragmentation via cleavage of the bond a and bond b with equal probability and poor stereochemical control on the part of the methyl group in subsequent cyclization via radical coupling (see intermediates **271** and **272**).

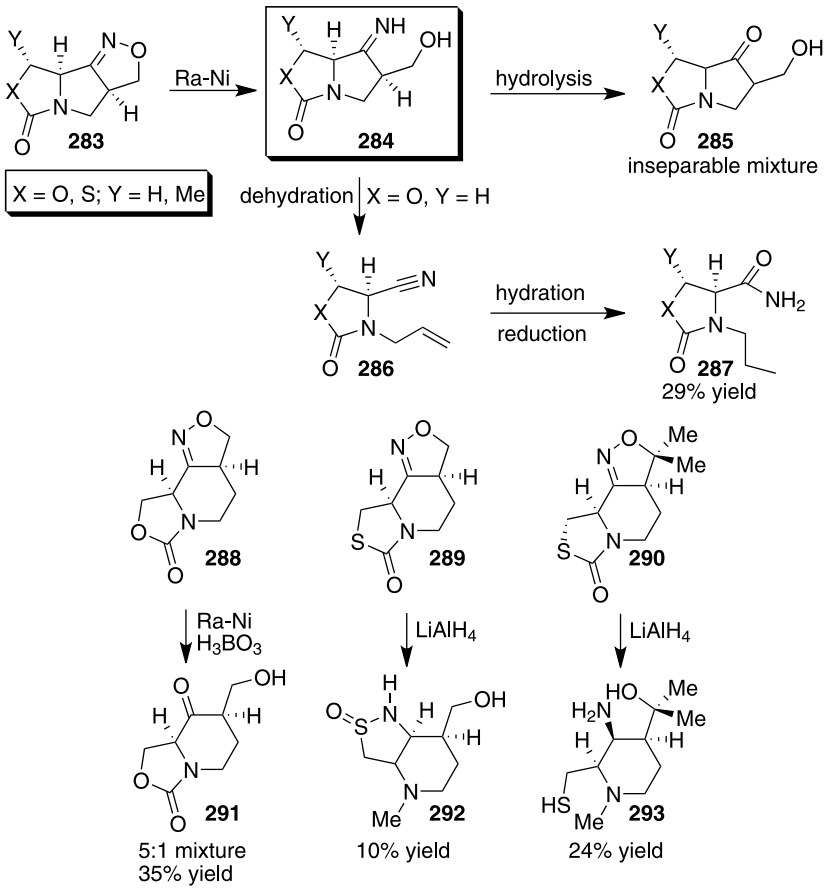
The thermal rearrangement of isoxazoline **273** provided 19-nor-10-azasteroid as a mixture of isomers **274a,b** in which the 9(11) isomer **274a** resulting from kinetic control of the reaction predominated over the 8(9) isomer **274b**.

Intramolecular 1,3-dipolar cycloaddition has been employed for the synthesis of various natural products as well. For instance, Mateos et al. reported a diastereoselective synthesis of the model insect antifeedant **281** related to 12-hydroxyazadiradione utilizing the intramolecular nitrile oxide cycloaddition (Scheme 65) [167]. The nitro compound **279** was synthesized from α-cyclocitral **278** in four steps. The cleavage of isoxazoline **280** was performed under three different conditions: Raney Ni-mediated cleavage in methanol-water-acetic acid provided the epimeric ketoalcohol **282** in ~5 : 3 ratio. While there was 100% selectivity in favor of the axial alcohol **282a** in the presence of Pd/C and boric acid, the selectivity was in favor of the equatorial alcohol **282b** when boric acid was replaced by acetic acid.

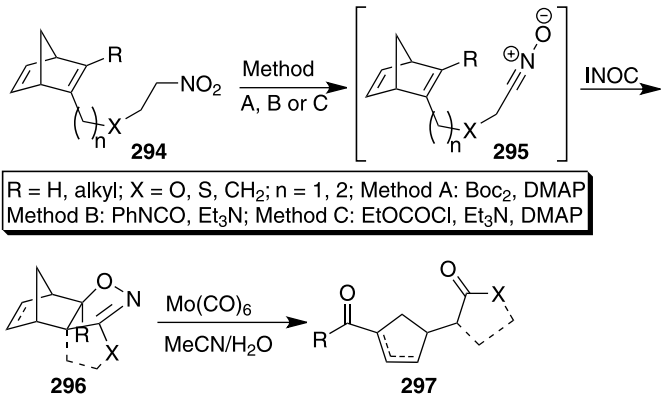


Scheme 65

Hassner and co-workers reported the cleavage of isoxazolines **283** (derived from INOC reaction of oximes) using Raney Ni to afford unsaturated nitriles **286** or ketoalcohols **285** (Scheme 66) [168]. Some of the derivatives of isoxazolines **283** led to amino azasugars that were glycosidase inhibitors. The reactions in Scheme 66 presumably proceed through the iminoalcohol **284** which on hydrolysis provides the hydroxyketone **285**. On the other hand,



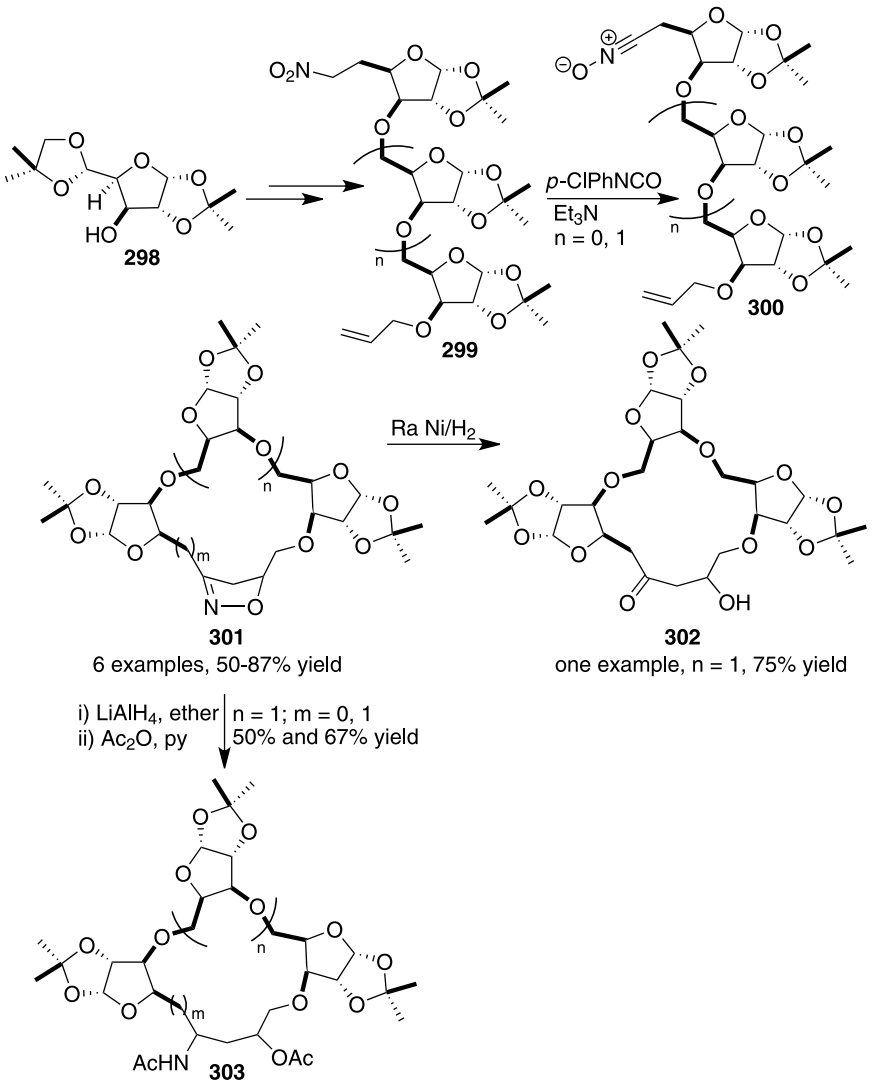
Scheme 66



Scheme 67

dehydration of the iminoalcohol **284** affords the nitrile **286** which could be hydrated and reduced to amide **287**. However, due to lack of stereoselectivity in the synthesis of substituted pyrrolidines **285**, the authors turned to synthesis of substituted piperidines **291**–**293** via cleavage of isoxazolines **288**–**290** under different conditions and obtained better stereochemical results.

Tam and co-workers reported highly regio- and stereoselective intramolecular 1,3-dipolar cycloaddition of norbornadiene-tethered nitrile oxide **295** for the construction of isoxazoline rings **296** fused to bicyclic framework



Scheme 68

(Scheme 67) [169, 170]. Among the three methods employed for the nitrile oxide generation, Boc_2O/DMAP method was found to be superior to the PhNCO/Et_3N and the $ClCO_2Et$/Et_3N/DMAP methods in terms of yield. The same group later reported $Mo(CO)_6$-mediated stereoselective transformation of the isoxazoline ring in **296** into substituted cyclopentene rings, cyclopentane rings, and attached-ring systems **297** [171]. The transformation involves a tandem N–O bond cleavage-retroaldol reaction.

Recently, Bhattacharjya and co-workers reported the synthesis of chiral isoxazolines **301** fused with 10–15 membered oxacycles via INOC sequence of 3,5′-ether linked pseudooligopentose derivatives **299**, which in turn were synthesized from carbohydrate precursors (Scheme 68) [172]. The nitrile oxides **300** were generated from oximes as well as from nitroalkanes **299**. The reductive cleavage of the isoxazoline rings performed under two different conditions, viz. Ra Ni and $LiAlH_4$ provided ketoalcohol **302** and amino alcohol derivative **303**, respectively, in good yields. The pseudooligosaccharide products are potential precursors to RNA analogues.

4 Conclusions

Nitroalkanes have emerged as valuable precursors to reactive 1,3-dipoles such as nitrile oxides and silyl nitronates which undergo facile cycloaddition with alkenes to afford isoxazolines. In recent years, the mechanism and application of different versions of this cycloaddition approach in the construction of the isoxazoline ring with high regio- and stereoselectivities have received considerable attention. This methodology has been employed for the synthesis of complex molecules, including biologically relevant compounds and natural products, by taking advantage of various modes of cleavage of the isoxazoline ring. The construction of the isoxazoline ring in enantiopure form via catalytic asymmetric approaches, application of the isoxazoline moiety as chiral ligands, etc., seem to be attractive objectives in future research in this area.

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Cycloaddition Reactions of Azides Including Bioconjugation

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Abstract Organic azides R-N_3, albeit being energy-rich and very reactive, are useful intermediates in organic synthesis. The cycloaddition reaction of azides with double and triple bonds to yield heterocyclic structures – albeit being discovered many centuries ago – has been evolved into a powerful tool in organic synthesis, material sciences and life sciences, and are thus covered in this review. In particular, the recent development of catalytic and therefore mild reaction conditions has led to an enormous increase of systematic investigation and novel applications.

Abbreviations

ABPP	Activity-based protein profiling
AIDS	Acquired Immune Deficiency Syndrome
ALDH	Aldehyde dehydrogenase
AZT	3′-Azido-3′-deoxythymidine
BAL	Backbone amide linker
BSA	*N*,*O*-Bis(trimethylsilyl)acetamide
CCK	Cholecystokinin
CE-1	Carboxylesterase-1
CoA	Coenzyme A
CPMV	Cowpea mosaic virus
CuAAC	Cu^{I}-catalyzed alkyne-azide coupling
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropyl-ethyl-amine
DMF	Dimethylformamide
DNA	Deoxyribonucleic acid
ECH	Enoyl CoA hydratase
Eth	Ethynylphenylalanine
FAMT	Formylaryloxymethyltriazole
GSTO	Glutathione *S*-transferase
HEPT	1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine
HPG	Homopropargylglycine
IC_{50}	Half maximal inhibitory concentration
IOAc	Intramolecular olefin azide cycloaddition
MTases	Methyltransferases
NMR	Nuclear magnetic resonance
Nu	Nucleophile
ODN	Oligodeoxyribonucleotide
OMPC	Outer membrane protein C
PAGE	Polyacrylamide gel electrophoresis
PCR	Polymerase chain reaction
PEG	Polyethylene glycol
PEO	Polyethylene oxide
PS	Phenylsulfonate
PTC	Phase transfer catalyst
Rh	Rhodamine
RNA	Ribonucleic acid
SAM	*S*-Adenosyl-L-methionine
SDS	Sodium dodecyl sulfate
TBAF	Tetrabutylammonium fluoride

TBDMS Tert-butyldimethylsilyl
TBTA Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine
TCEP Tris(2-carboxyethyl)phosphine
TFA Trifluoroacetic acid
THF Tetrahydrofurane
TMS Trimethylsilyl
TMSA Trimethylsilyl azide
Ts Toluenesulfonyl
UCP Uncoupling protein

1 Introduction

Organic azides $R–\overset{\ominus}{N}–\overset{\oplus}{N}\equiv N$, albeit being energy-rich and very reactive, are useful intermediates in organic synthesis [1]. They are bifunctional, reacting with electron-deficient compounds (electrophiles) at N(1) and with electron-rich compounds (nucleophiles) at N(3) [1]. The three nitrogens can be retained during the reaction, but cleavage to form nitrene compounds is also common. The bifunctionality of azides also enables them to undergo 1,3-dipolar cycloaddition reactions.

After organic azides were discovered by Peter Griess more than 140 years ago, numerous applications have been developed. Particularly in more recent times, completely new perspectives have been developed for their use in peptide and combinatorial chemistry as well as in heterocyclic synthesis. In this non-comprehensive review [2–4], the fundamental characteristics of azide cycloaddition chemistry and current developments in life and material sciences are presented.

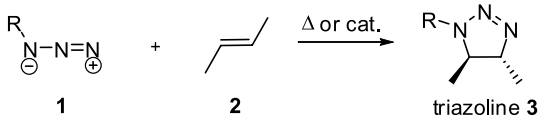
1.1 Properties of Azides

SAFETY: [1] Whereas ionic azides such as sodium azide are relatively stable, carbon-bound or heavy-metal azides are subject to thermal, sometimes explosive, decomposition. For organic azides to be manipulatable or nonexplosive, the number of nitrogen atoms must be lower than that of carbon atoms and $(N_C + N_O)/N_N = 3$ (N = number of atoms of C, O, N). The stability of the azido group is somewhat enhanced by the aromatic nucleus, however, the presence of functional groups in the *ortho* position often leads to decreased stability. Pyrolysis usually occurs with moderate evolution of nitrogen; however, rapid heating may produce an explosion. Nitrogen was liberated at temperatures as low as 85 °C for *o*-nitrophenyl azide forming a furazane while most of the aromatic azides decompose in the range of l50 to 200 °C. Strong Brønsted or Lewis acids such as sulfuric acid, perchloric acid,

or boron trifluoride, may also release nitrogen from aryl azides, the reaction mechanism usually being more complicated. Exposure to short-wavelength irradiation leads to formation of nitrenes [1]. Some organic and other covalent azides are classified as toxic and highly explosive, and appropriate safety measures must be taken at all times.

2
Cycloaddition Reactions to C–C Double Bonds

The addition of a 1,3-dipole to an alkene for the synthesis of five-membered rings is a classic reaction in organic chemistry and is used for the preparation of molecules of fundamental importance. The 1,3-dipolar – mostly stereospecific – cycloaddition of an azide **1** with an alkene **2** leads to the formation of a triazoline **3** (Scheme 1).



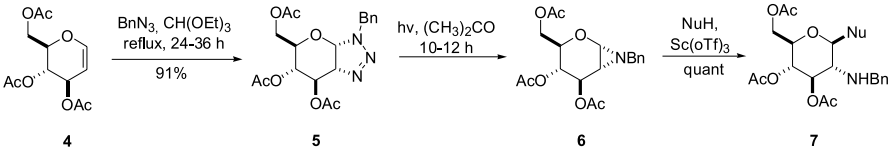
Scheme 1 1,3-Dipolar cycloaddition of azide **1** and alkene **2**

The reaction is an important synthetic route to triazolines and their derivatives [5–7] such as cyclic imines or aziridines and is hence a valuable technique in the synthesis of heterocycles [8]. The reaction rate is dependent on the dipolarophile. Whereas strained olefins, such as norbornene, react readily, terminal alkenes react extremely slowly [9].

2.1
Thermal (Uncatalyzed) Reactions

2.1.1
Intermolecular Cycloaddition Reactions of Azides

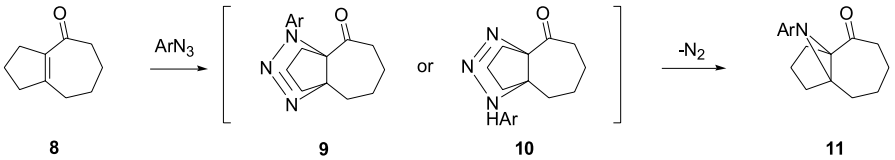
Azides can behave differently under different reaction conditions. Organic azides react in uncatalyzed thermal cycloaddition reactions with olefins to form 1,2,3-Δ^2-triazolines. A useful application of a dipolar cycloaddition was shown by Finney et al. who found that glycals with electron withdrawing protecting groups (e.g., **4**) can undergo efficient cycloaddition reactions with electron-rich azides to form stable triazoline **5** [10]. A quantitative photochemical conversion carried out in acetone leads to the corresponding aziridine **6**, which reacts with nucleophiles under mild conditions to afford aminoglycoside product **7** in good yields (Scheme 2).



Scheme 2 New access to aminoglycosides via triazoline [10]

Kover and co-workers demonstrated how to use 1,3-dipolar cycloaddition reactions in a protection cycle to distinguish between the two double bonds in (+)-limonene [11].

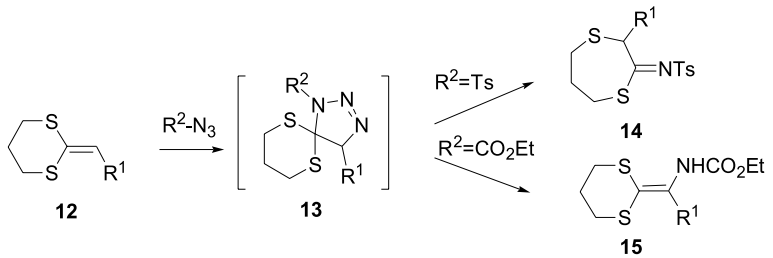
Synthesis of 11-aryl-11-aza[5.3.1.]propellan-2-one (**11**) was achieved by the intermolecular cycloaddition of the bicyclodecenone **8** with an aryl azide (Scheme 3) [12]. The aziridine **11** was obtained through the two possible intermediates **9** or **10.**



Ar=Ph, *p*-MePh, *p*-BrPh

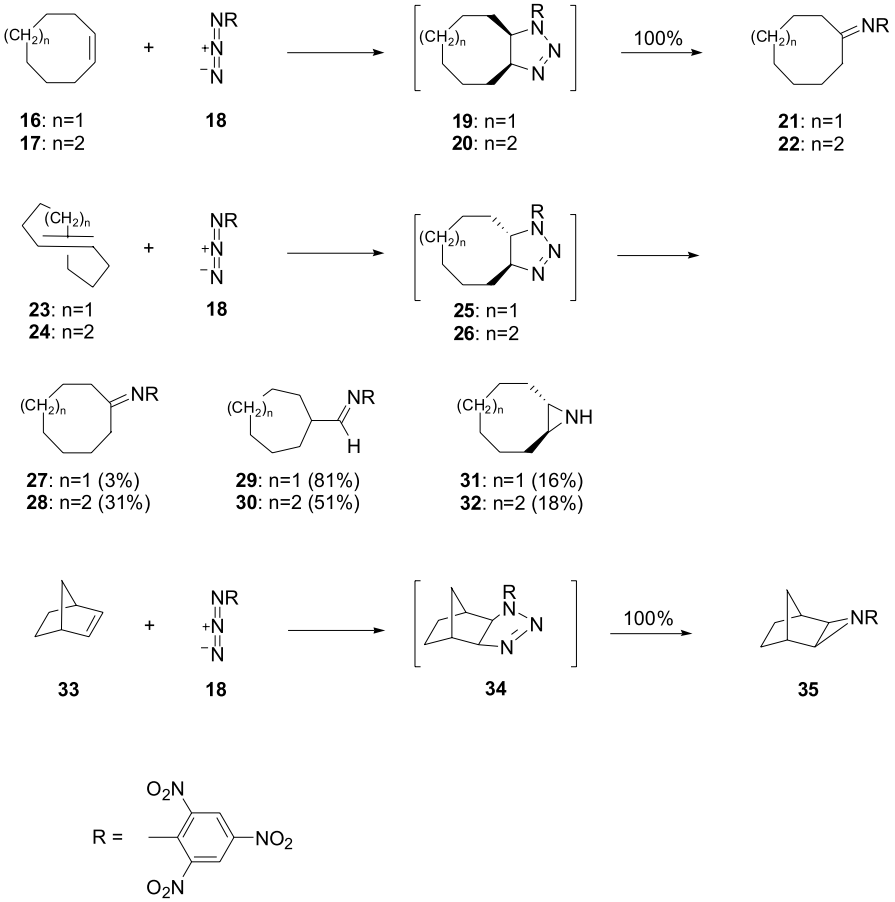
Scheme 3 1,3-Dipolar-cycloaddition as protecting cycle [12]

Gallagher et al. described the cycloaddition of electron-deficient azides with ketene-(*S*,*S*)-acetals **12** [13]. Depending on the azide compound, the unstable intermediate **13** rearranged in order to afford **14** or **15** in moderate yields (Scheme 4).



Scheme 4 Cycloaddition of electron-deficient azides with ketene-(*S*,*S*)-acetals **12** [13]

Shea et al. investigated whether strain involved in alkenes affects reactivity and regiochemistry of the intermolecular 1,3-dipolar cycloaddition reaction [14]. Therefore, the addition of picryl azide (**18**) with a series of mono- and bicyclic olefins including *trans*-cycloalkenes and bridgehead alkenes was studied (Scheme 5). In the cases of *cis*-cyclooctene (**16**) and *cis*-cyclononene (**17**), decomposition of the initially formed cycloadducts **19** and **20** followed

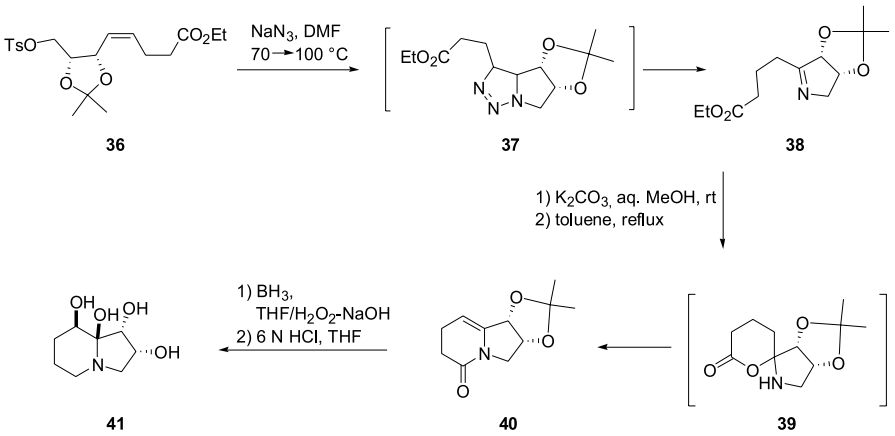


Scheme 5 Effect of strain on reactivity and regiochemistry [14]

by a 1,2-hydride shift gave compounds **21** and **22**, respectively. When cycloaddition reactions were performed with *trans*-cyclooctene (**23**) and *trans*-cyclononene (**24**), the corresponding cycloadducts **25** and **26** both underwent 1,2-hydride and 1,2-alkyl migration to give ketimines **27** and **28** and aldimines **29** and **30**, respectively. A small proportion of aziridines **31** and **32** was also obtained. The cycloaddition of picryl azide (**18**) and norbornene (**33**) to triazoline **34** followed by loss of nitrogen gave the exo aziridine **35** in very good yield. Furthermore, the reactivity of strained olefins is significantly higher than that of simple unstrained cycloalkenes. The reactivity of *trans*-cyclooctene (**23**) is even higher than that of norbornene (**33**), which reacts much faster than cyclohexene. According to these studies, it was confirmed that the strain involved in these alkenes affects both the reactivity and the regiochemistry of the cycloaddition reaction.

2.1.2
Intramolecular Cycloaddition Reactions of Azides

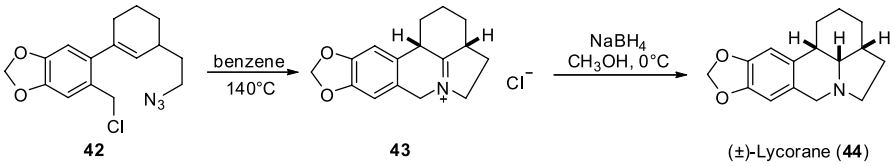
It is well known that alkyl azides also behave as 1,3-dipoles in intramolecular thermal cycloaddition reactions. The formation of two carbon-nitrogen bonds leads to triazolines, which are usually not stable. They decompose after the loss of nitrogen to aziridines, diazo compounds, and heterocyclic imines. There are a limited number of examples reported in which the triazoline was isolated [15]. The dipolar cycloaddition methodology has been extremely useful for the synthesis of many natural products with interesting biological activities [16]. In recent years, the cycloaddition approach has allowed many successful syntheses of complex molecules which would be difficult to obtain by different routes. For instance, Cha and co-workers developed a general approach to functionalized indolizidine and pyrrolizidine alkaloids such as (+)-crotanecine [17] and (–)-slaframine [18]. The key step of the enantioselective synthesis of (–)-swainsonine (**41**), starting from **36**, involves the construction of the bicyclic imine **38** by an intramolecular 1,3-dipolar cycloaddition of an azide derived from tosylate **36**, as shown in Scheme 6 [19].



Scheme 6 Enantioselective synthesis of (–)-Swainsonine (**41**) [19]

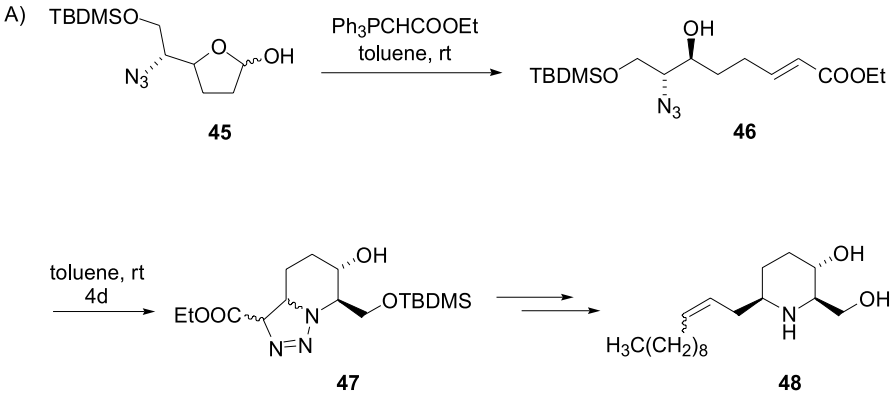
Using ω-chloroalkenes (e.g., **42**) in 1,3-dipolar cycloaddition reactions, Pearson et al. described the synthesis of several alkaloids [20–22]. The reaction proceeds by an intramolecular cycloaddition of an azide onto an alkene, producing an intermediate triazoline. Fragmentation of the triazoline and rearrangement to a monocyclic imine occurs, which is internally *N*-alkylated by the alkyl chloride, resulting in iminium ion **43**. Reduction with sodium borohydride leads to the racemic lycorane (**44**).

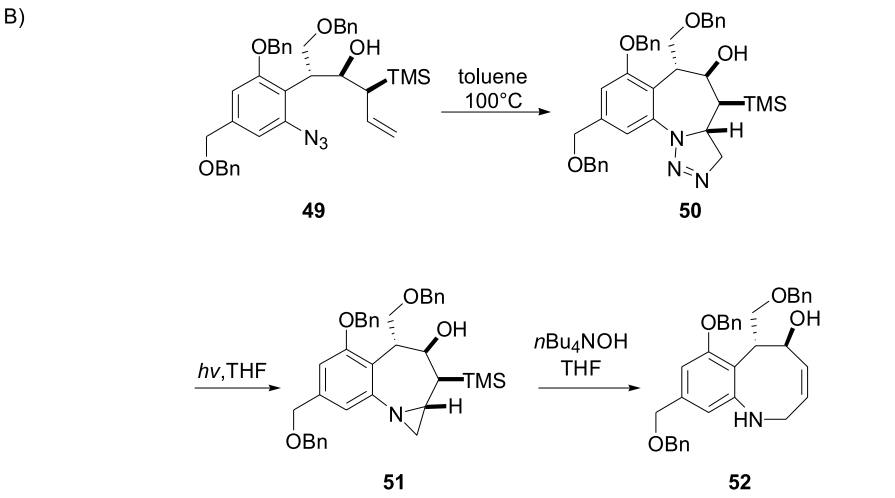
A domino Wittig intramolecular cycloaddition has been used in total synthesis several times [15, 23, 24]. Herdeis et al. showed an application of



Scheme 7 Synthesis of (±)-Lycorane (**44**) [21]

a domino Wittig [3+2]-cycloaddition reaction in the stereoselective synthesis of the *Propsis* alkaloid (+)-desoxoprosophylline (**48**) (Scheme 8A). Key intermediate **45** was subjected to a Wittig reaction using (ethoxycarbonyl-



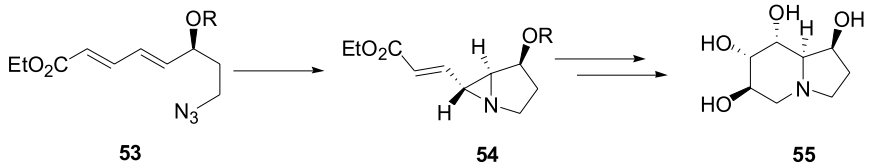


Scheme 8 **A** Stereoselective synthesis of the *Propsis* alkaloid (+)-desoxoprosophylline (**48**), **B** total synthesis of (±)-FR66979 (**52**) [23, 25]

methylene) triphenylphosphorane in dry toluene for 80 minutes followed by a [3+2]-cycloaddition, resulting in **48** as a diastereomeric mixture in 98% after 4 days.

Ciufolini and co-workers demonstrated the use of 1,3-dipolar azide-olefin cycloaddition reactions in the total synthesis of (±)-FR66979 (**52**) [25], an antitumor agent which is structurally related to the mitomycins [26]. Thus, the triazoline **50** was obtained as a single diastereomer by smooth cycloaddition of the activated double bond and the dipole in **49** by heating in toluene. Brief photolysis of **50** provided aziridine **51**, which fragmented to **52** (Scheme 8B). Other intramolecular azide-alkene cycloaddition in natural product synthesis is illustrated by a number of examples [27–32].

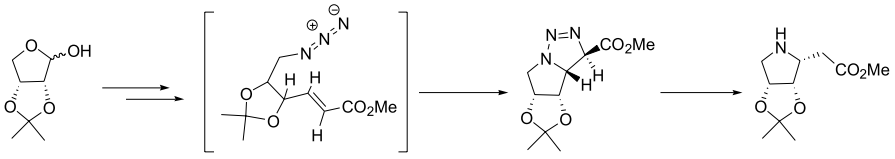
In many 1,3-dipolar cycloaddition reactions, the initially formed stereogenic center(s) will be destroyed in the following rearrangement. In the synthesis of 6,7-di-*epi*-castanospermine (**55**) from **53**, the aziridine **54** was obtained as the sole product stereoisomer (Scheme 9) [33].



53 **54** **55**

Scheme 9 Synthesis of 6,7-di-*epi*-castanospermine (**55**) [33]

The intramolecular cycloaddition of azides with alkenes has also been used for the synthesis of chiral hydroxypyrrolidines [34]. In the intramolecular 1,3-dipolar cycloaddition shown in Scheme 10, the azide **57** derived from 2,3-*O*-isopropylidene-D-erythrose (**56**) gave triazole **58**. Ring opening followed by hydrogenolysis gave the diastereomeric pure hydroxypyrrolidine **59**.

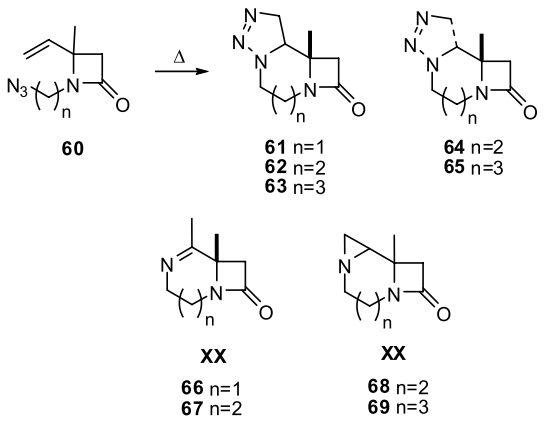


56 **57** **58** **59**

Scheme 10 Synthesis of chiral hydroxypyrrolidines [34]

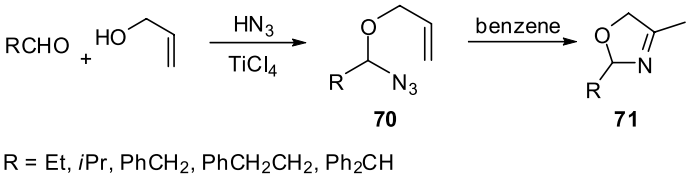
Hassner and co-workers have shown that the intramolecular azide-alkene cycloaddition reactions of azido vinyl β-lactams primarily lead to *cis* fused triazolines. The triazoline **61**, fused to a 6-membered ring, was formed exclusively as the *cis*-fused isomer and decomposed on treatment with silica gel to imine **66**. On the other hand, the 8-membered ring fused triazoline **63** which was isolated as a *cis:trans* mixture, on exposure to silica, produced only aziri-

dine **69**, while the triazoline **62**, fused to a 7-membered ring, gave a mixture of imine **67** and **68** aziridine (Scheme 11) [35].



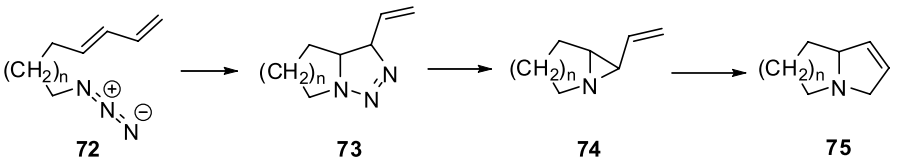
Scheme 11 A synthetic route to β-fused-Lactams via IOAC

A new simple synthetic route to 2,5-dihydrooxazoles **71** by cycloaddition of allyl azido ethers **70** via triazolines was shown by Hassner et al. [37]. Earlier, they demonstrated that α-azido ethers can be easily prepared from aldehydes using an alcohol, hydrazoic acid and titanium tetrachloride as well as the fact that thermolysis of azido ethers in the absence of a double bond forms imidates [35, 36]. Using the above mentioned facts, the allyl azido ethers **70** were synthesized in good yields employing an aldehyde, an allyl alcohol and HN_3 in a 1:3:9 ratio in presence of a Ti catalyst (Scheme 12). Allyl azido ethers **70**, on thermolysis in benzene, proved to be ideal substrates for the formation of 2,5-dihydrooxazoles **71** in 66–90% yield. To show that oxazolines are formed via triazolines and not via an independent nitrene pathway, thermolysis of **70** was followed by ^{1}H NMR in hexadeuteriobenzene at 70 °C.



Scheme 12 A simple synthetic route to 2,5-dihydrooxazoles **61** [37]

Many classes of alkaloids reveal a pyrrolizidine skeleton as a key structural element. Hudlicky et al. and Pearson et al. demonstrated the applicability of 1,3-dipolar cycloaddition of an azide with an alkene moiety in a conjugated diene to generate pyrrolizidines [38–42]. The triazoline **73** was formed by an



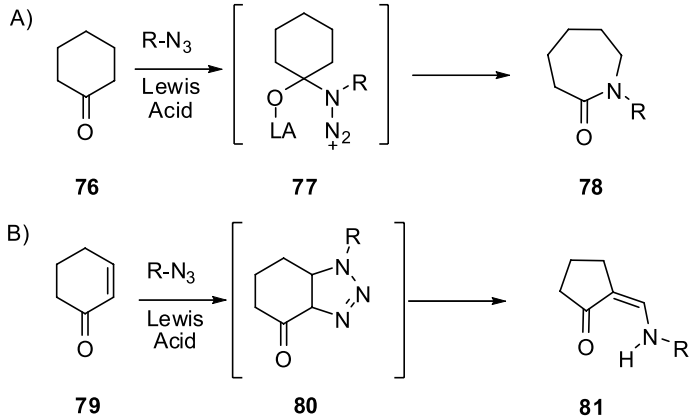
Scheme 13 Pyrrolizidine alkaloids via [4+1]-cycloaddition reactions [38–42]

intramolecular 1,3-dipolar cycloaddition of the azidodiene **72** followed by the elimination of N_2 in order to give aziridine **74** (Scheme 13). Rearrangement of the aziridine resulted in the bicyclic 3-pyrroline **75**. Furthermore, a novel approach to piperazines by an intramolecular [2+3]-addition of an azide to a C=C double bond was recently described [43].

2.2 Catalyzed Reactions

2.2.1 Intermolecular Cycloaddition Reactions of Azides

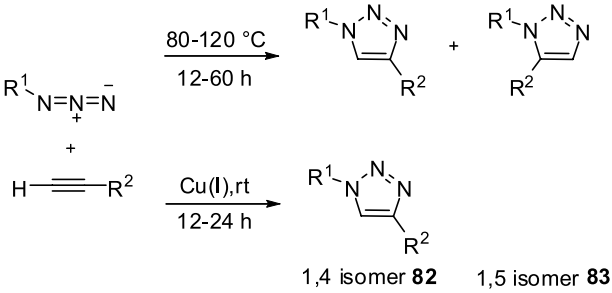
About 15 years ago, Aube et al. reported that alkyl azides undergo Lewis acid-mediated reactions with ketones **76** to give the corresponding lactams **78** via **77** (Azido-Schmidt reaction; Scheme 14A) [44–48]. However, this reaction pathway does not proceed when α,β-unsaturated ketones are used. It was recently shown that Lewis acid-activated enones like **79** undergo a [3+2] cycloaddition with alkylazides, likely via an 1,2,3-triazoline intermediate **80**, to give the corresponding enaminone **80** (Scheme 14B) [49].



Scheme 14 **A** Azido-Schmidt reaction. **B** Lewis acid-mediated reactions of alkylazides with α,β-unsaturated ketones [49]

3
Cycloaddition Reactions to C–C Triple Bonds

The 1,3-dipolar cycloaddition of organic azides to alkynes developed in the 1960s by Huisgen is a very important organic reaction and is the most efficient route to synthesize 1,2,3-triazoles [5]. Thermal cycloaddition affords both 1,4- and 1,5-regioisomers **82** and **83** due to the close activation energies for the concerted process leading to both isomers (Scheme 15). Thus, only following the recent discovery of the advantages of Cu^{I}-catalyzed alkyne-azide coupling (CuAAC), independently reported by the Sharpless [50] and Meldal [51] groups, did the main benefits of this cycloaddition become clear. Cu^{I} catalysis dramatically improves regioselectivity, thereby exclusively affording the 1,4-regioisomer **82**.



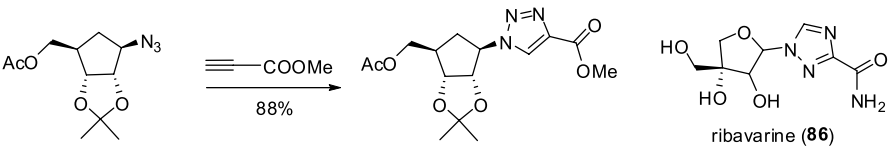
Scheme 15 The 1,3-dipolar cycloaddition of an alkyne and an azide to give a 1,2,3-triazole. Under thermal conditions the cycloaddition is non-regiospecific, whereas complete 1,4-regioselectivity is achieved under Cu(I)-catalyzed conditions [5, 51]

3.1
Thermal (Uncatalyzed) Reactions

Prior to the use of copper(I), the cycloaddition of azides with terminal acetylenes usually required elevated temperatures for prolonged periods of time. A number of strained or electronically activated alkynes can react with organoazides at room temperature, whereas with many other alkynes, the reaction must be carried out at higher temperatures when no catalyst is present. Typically, conditions involved refluxing toluene or carbon tetrachloride for 10–48 h. Already in 1965, Huisgen and co-workers reported on the addition of arynes to azides leading to benzotriazoles. A copper free, strain-promoted [3+2]-azide-alkyne cycloaddition for covalent modification of biomolecules in living systems was introduced by Bertozzi et al. [52]. Due to the toxicity of copper to bacterial and mammalian cells, the application of CuAAC is limited to the selective modification of living cells.

3.1.1 Intermolecular Cycloaddition Reactions of Azides

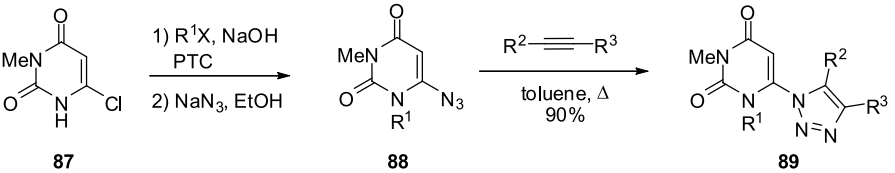
The preparation of **85**, a structurally diverse analog of carbocyclic ribavarine (**86**), was reported using an intermolecular 1,3-dipolar cycloaddition reaction of cyclopentyl azide **84** with methyl propiolate [53].



84 **85**

Scheme 16 Synthesis of ribavarine analog **75** via an intermolecular 1,3-dipolar cycloaddition reaction [53]

An efficient synthesis of the 1-allyl-6-(1′,2′,3′-triazolyl) analog **89** of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT), an anti-human immunodeficiency virus (HIV) reverse transcriptase inhibitor, was reported using an intermolecular 1,3-dipolar cycloaddition of the azide **78** with acetylenes (Scheme 17) [54]. Azidouracil, when refluxed with acetylene in toluene, gave the corresponding triazoles **89** in excellent yield (Scheme 17).



87 **88** **89**

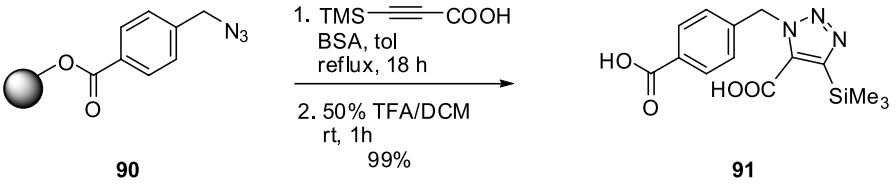
R^1 = Allyl, Me
$R^2 = R^3 = CO_2Me$
R^2 =Ph, R^3= H

Scheme 17 Synthesis of the 1-allyl-6-(1′,2′,3′-triazolyl) analog **89** of 1-[2-(hydroxyethoxy)-methyl]-6-(phenylthio)thymine (HEPT) [54]

A straightforward synthesis of fused dihydrotriazolo[1,5-α]pyrazinones and triazolobenzodiazepines by sequential Ugi/alkyne-azide cycloaddition reactions was recently demonstrated by Djuric et al. [55]. The coupling of the Ugi multi-component reaction with the intramolecular alkyne-azide cycloaddition provides access to highly functionalized heterocyclic ring systems in just two steps.

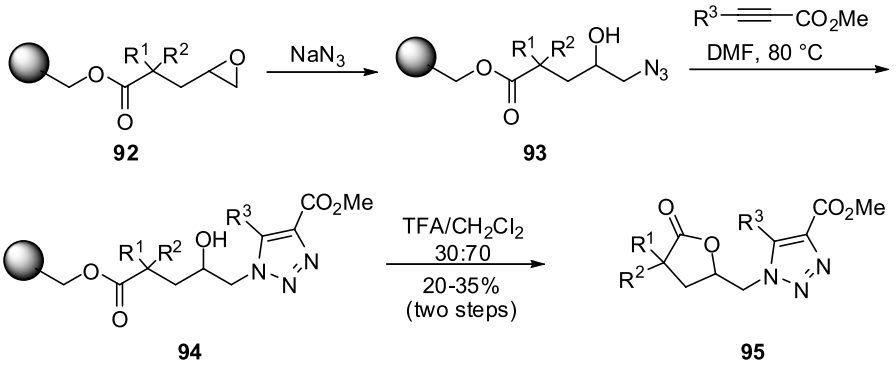
The regiochemically-directing effect of the trimethylsilyl group [56] for the preparation of 1,5-trisubstituted 1,2,3-triazole via 1,3-dipolar cycloaddition on solid-phase was recently described [57]. Adding BSA (bis(trimethylsilyl)-

acetamide) protects against desilylation and decarboxylation and the 1,5-triazole **81** was obtained in near quantitative yield (Scheme 18).



Scheme 18 Trimethylsilyl-directed 1,3-dipolar cycloaddition reactions in the solid-phase synthesis of 1,2,3-triazoles [57]

Furthermore, other solid phase variants of this reaction with immobilized azides have been used for the preparation of substituted 1,2,3-triazoles [58]. In the example shown in Scheme 19, the final product **95** was obtained by subsequent cleavage and cyclization.

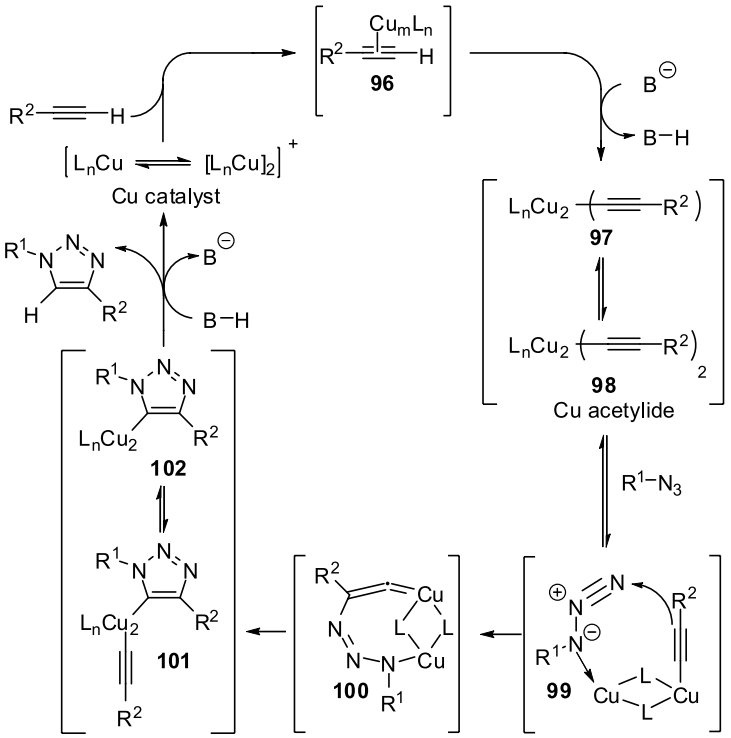


Scheme 19 Synthesis of 1,2,3-triazoles on a polystyrene support according to David and co-workers [58]

3.2 Catalyzed Reactions

The turning point for the above mentioned 1,3-dipolar cycloaddition occurred with the independent discovery that copper(I) not only promotes the speed of the reaction (often referred to as click reaction), but also improves regioselectivity. The copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) of terminal alkenes with organic azides to yield 1,4-disubstituted 1,2,3-triazoles discovered by Meldal [51] and Sharpless [50] exhibits remarkably broad scope and exquisite selectivity [59, 60]. The most prominent application of click reactions in recent years has been in drug research [61, 62],

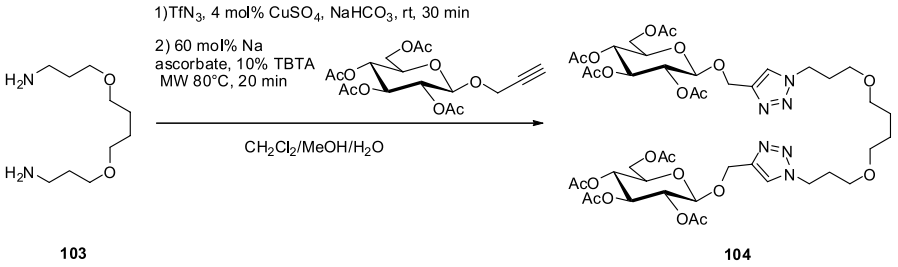
bioconjugate chemistry [63–66] and material science [67–74]. Advantages are high reaction yields, simple reaction and purification conditions, stability to a variety of solvents and tolerance of most functionalities. The reaction easily occurs in aqueous media in a broad pH area (4–12) and is thus extremely biocompatible. Although it was long established that the thermal dipolar cycloaddition of azides and alkynes occurs through a concerted mechanism, DFT calculations on monomeric copper acetylide complexes indicate that the concerted mechanism is strongly disfavored relative to a stepwise mechanism (Scheme 20) [72–74]. Based on an earlier precedent of Cu^{I} insertion into terminal alkynes and experimental evidence indicating that internal alkynes show no activity in this reaction, researchers propose that a stepwise catalytic cycle begins with the formation of a Cu^{I} acetylide species via π complex **96**. Following the formation of the active copper acetylide species **98**, azide displacement of one ligand generates a copper acetylide-azide complex, such as the dicopper species **99**. Complexation of the azide activates it towards nucleophilic attack of acetylide generating metallocycle **100**. Protonation of triazole-copper derivative **102** followed by dissociation of the product ends the reaction and regenerates the catalyst.



Scheme 20 Proposed outline of species involved in the catalytic cycle [67–71]

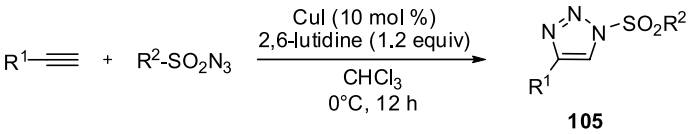
3.2.1
Intermolecular Cycloaddition Reactions of Azides

Recently, Wittmann and co-workers reported the one-pot procedure for diazo transfer and azide-alkyne cycloaddition reaction. As shown in Scheme 21, the divalent glycoconjugate **104** was obtained in excellent yield from amine **103** without the need for isolation of the azide intermediate. Similarly, Moses et al. reported on the efficient conversion of aromatic amines into 1,2,3-triazoles [75].



Scheme 21 Synthesis of divalent glycoconjugate **94** using a one-pot procedure [75]

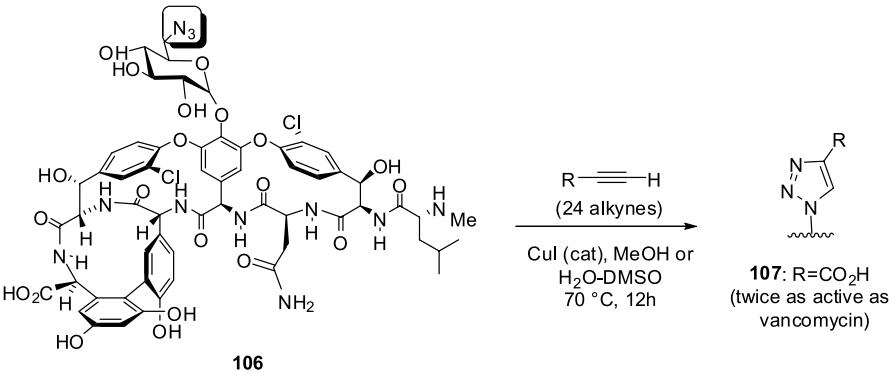
The reaction of sulfonyl azides with terminal alkynes is an interesting exception. Whereas aryl and alkyl azides react with activated alkynes to give the corresponding 1,2,3-triazoles, intermediate sulfonyltriazoles result in the formation of different products. In the presence of amines, *N*-sulfonyl azides are converted to *N*-sulfonyl amidines, whereas under aqueous conditions, *N*-acylsulfonamides are the major products [76–78]. Nevertheless, Fokin et al. reported conditions for the successful formation of *N*-sulfonyl-1,2,3-triazoles **105** shown in Scheme 22 [79].



Scheme 22 Cu-catalyzed cycloaddition of terminal alkynes and sulfonyl azides [79]

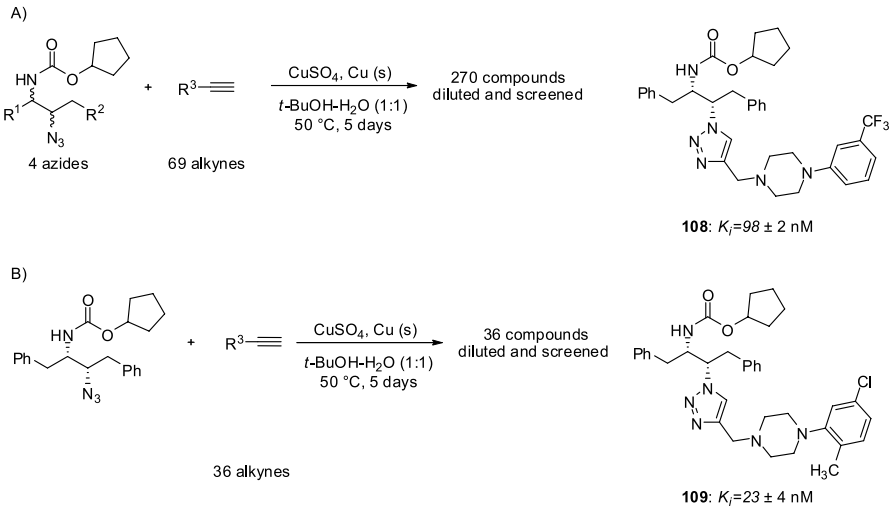
The modification and biological profiling of potentially useful bioactive natural products is a very important goal. By applying CuAAC in the last step of derivatization, Walsh et al. prepared a library of the glycopeptide antibiotic tyrocidine [80].

Due to the fact that biological activity is often modulated by their glycosylation pattern [81], the azide-alkyne cycloaddition was also used in glycorandomization studies performed on Vancomycin by Thorsen and co-workers (Scheme 23) [82].



Scheme 23 Applying CuAAC to create a small library of vancomycin analogs [82]

HIV-1-protease has been recognized as an important target for the inhibition of viral replication. In addition to seven inhibitors that have been approved by the FDA since 1995, a number of others are currently undergoing clinical evaluation; however, their success has been undermined by the rapid mutation of the virus. Wong et al., for example, prepared a focused library of about 50 compounds utilizing CuAAC as the last assembly step [61]. A recent study disclosed a novel series of potent HIV-1 protease inhibitors that have been developed [83]. CuAAC was used to unite a focused library of azide-containing fragments with a diverse array of functionalized alkyne containing building blocks (Scheme 24). In combination with the direct screening of



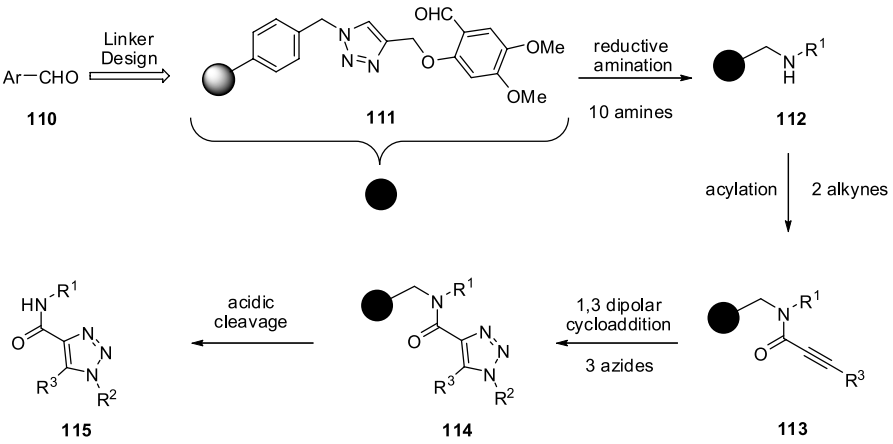
Scheme 24 A novel series of HIV-1 protease inhibitors discovered via the Cu(I)-catalyzed synthesis of 1,2,3-triazoles [84]

the crude reaction products, this method led to the rapid identification of a lead structure and readily enabled optimization of both azide and alkyne fragments. After direct screening of the crude reaction products, a lead structure, **108** with K_I = 98 nM, was identified. The optimization of both azide and alkyne fragments proved equally simple (e.g., **109**; K_I = 23 nM).

Also, copper in charcoal (Cu/C) is found to be an active catalyst for effecting click reactions between organic azides and terminal alkynes [84]. Rates of cycloaddition are dramatically increased when carried out in the presence of triethylamine or using microwave assistance. There is no sensitivity to air or moisture and the catalyst can be recycled several times without loss of activity or selectivity for the 1,4-adduct.

Ruthenium(II) complexes were recently reported to catalyze the cycloaddition reaction of terminal as well as internal alkynes, forming 1,5-disubstituted and 1,4,5-trisubstituted-1,2,3-triazoles which cannot be obtained by copper catalysis [85, 86].

Although solution-phase click chemistry has demonstrated the power of this transformation, the success on solid phase coupled with combinatorial chemistry makes this cycloaddition an essential tool in drug discovery [74]. According to preliminary research results, solid phase CuAAC shows little sensitivity to reaction conditions, resin type or subsequent transformations, though alkyne homocoupling may prove problematic. Despite limitation, solid-phase alkyne-azide coupling has the potential to generate numerous molecules of diverse functionality [87–89]. CuAAC on solid supports was also used for the synthesis of multiple labeled-carbohydrate oligonucleotides [90] and highly functionalized peptoid oligomers [91]. Gmeiner and co-workers, for example, applied the click chemistry derived FAMT (formylaryloxymethyltriazole) resin (**111**) for a parallel solid supported



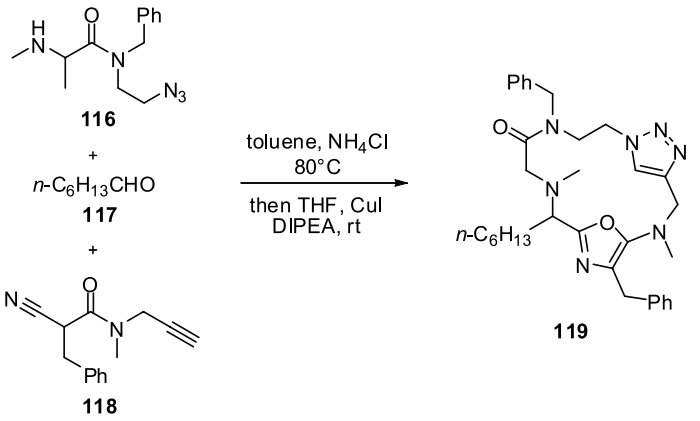
Scheme 25 Solid-phase supported synthesis of 60 triazoles **115** [92]

synthesis (Scheme 25) [92]. A library of 60 test compounds **115** revealing three points of diversity was generated by a four-step BAL-based (backbone amide linker) strategy including reductive amination, acylation with alkyne derivatives, 1,3-dipolar cycloaddition reaction with azides and TFA-induced cleavage. The target compounds were screened for neuroreceptor binding.

3.2.2 Intramolecular Cycloaddition Reactions of Azides

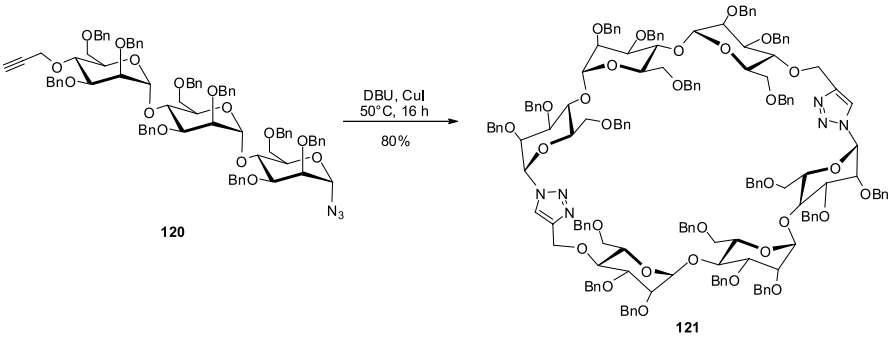
Despite the biological significance of the triazole moiety and the success of intermolecular triazole formation, intramolecular alkyne-azide coupling remains surprisingly limited. On a macromolecular scale, intramolecular triazole formation can occur on specially synthesized DNA molecules [93] by cyclodimerization of solid-phase bound suitably functionalized peptides [94] or on copper surfaces to induce adhesion [95]. There are just a few traditional examples on macrocycloadditions [96–98].

A one-pot synthesis of macrocycles by a domino three-component reaction and [3+2] cycloaddition was investigated by Zhu et al. [99]. By combining three appropriately designed simple substrates, a programmed sequence involving an α-isocyano acetamide-based three-component reaction followed by a copper-catalyzed cycloaddition of alkyne and azide took place to afford macrocycles **119** in moderate to good yields (Scheme 26).



Scheme 26 One-pot synthesis of macrocycles by a three-component reaction/[3+2]-cycloaddition reaction [99]

Successful dimerization by intramolecular Cu^{I}-catalyzed cycloaddition yielded macrocycle **121** in 80% yield (Scheme 27) and was reported by Gin and co-workers [100].



Scheme 27 Dimerization of the trisaccharide **120** to macrocycle **121** [100]

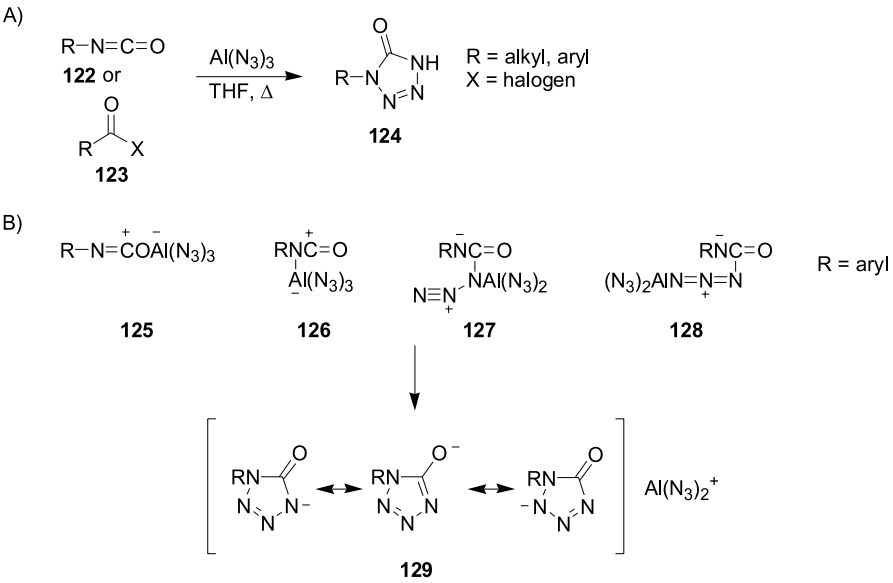
4
Cycloaddition Reactions to X=Y Double Bonds

Cycloaddition reactions of inorganic or organic azides to X=Y double bonds in organic molecules are limited to heterocumulenes like isocyanates, isothiocyanates and carbodiimides. To the best of our knowledge, no catalyzed reactions are known concerning the cycloaddition reaction between azides and substances with X=Y double bond thus far, meaning that all reactions discussed in the following chapter are performed thermally.

4.1
Addition of Azides to Isocyanates

In 1956, Hattori and co-workers established that aluminum azide adds to alkyl isocyanates or acid chlorides in tetrahydrofuran to afford 1-alkyl-Δ^2-tetrazoline-5-ones in excellent yields [101]. Three years later, Horwitz and co-workers reported on the synthesis of 1-aryl-Δ^2-tetrazoline-5-ones by reaction of aryl isocyanates with a mixture of sodium azide and aluminum chloride in tetrahydrofuran at reflux temperature [102]. The in situ produced aluminum azide adds to the N=C-bond of the corresponding isocyanate **122** and yields the 1-substituted Δ^2-tetrazoline-5-one **124**. According to this method, different 1-substituted Δ^2-tetrazoline-5-ones **124** were synthesized by reaction of phenyl isocyanate and further 1-*p*-substituted phenyl isocyanates with aluminum azide. In addition, acyl halides **123**, like acetyl chloride and benzoyl chloride, were converted to 1-methyl and 1-phenyl-Δ^2-tetrazoline-5-one with aluminum azide under the same conditions (Scheme 28A). It is assumed that in the initial step of the reaction, aluminum azide is able to coordinate to the aryl isocyanate by four pathways, forming an aluminum salt **129**. The first two possibilities (Scheme 28B; **125** and **126**) require the separation of an azide ion from the complex, recombination at the electrophilic carbon atom followed

by cyclization to **129.** In contrast, the second pair (Scheme 28B; **127** and **128**) should afford the aluminum salt **129** by direct cyclization. The advantage of the use of aluminum azide against sodium azide is the fact that the aluminum ion polarizes the azide group much more than the sodium ion. This in turn leads to the easier separation of an azide ion from the aluminum salt that is necessary for ring formation by cyclization (Scheme 28B) [102].



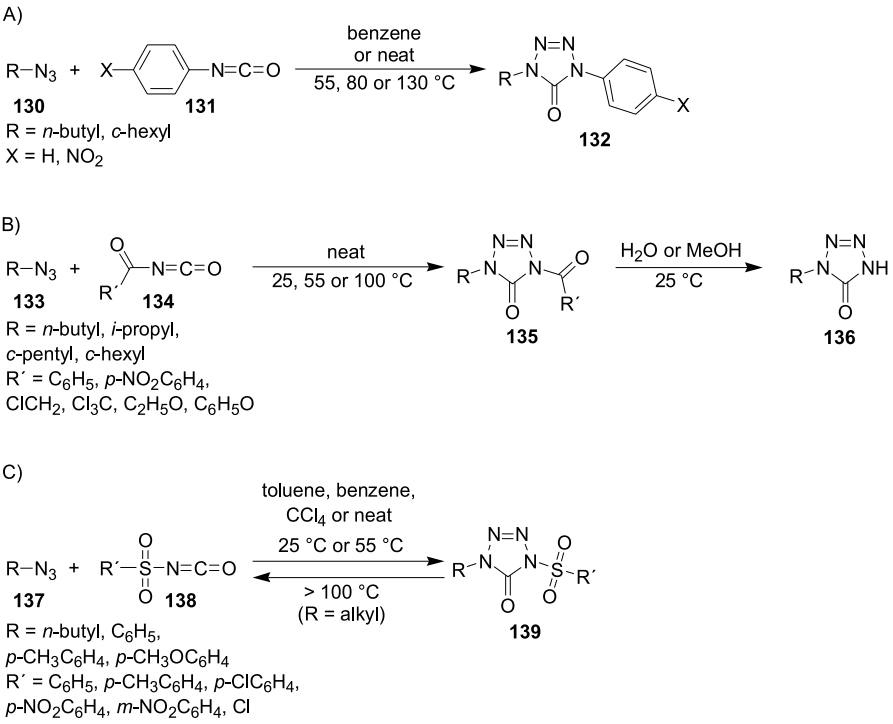
Scheme 28 **A** Synthesis of 1-substituted Δ^2-tetrazoline-5-ones **124** from isocyanates **122** or acyl halides **123** by use of aluminum azide [101, 102], **B** Four possible aluminum azide salt intermediates of aryl isocyanates and their cyclization to the aluminum salt of 1-substituted Δ^2-tetrazoline-5-ones **129** [102]

The disadvantage of this method for synthesizing 1-aryl-substituted Δ^2-tetrazoline-5-ones is the fact that three equivalents of sodium azide per equivalent isocyanate are required [102]. To circumvent this drawback, a process for the generation of 1-aryl- and 1-alkyl-substituted Δ^2-tetrazoline-5-ones was developed that uses equimolar amounts of sodium azide, aluminum chloride and the corresponding isocyanate in DMF as solvent. Heating of this three component mixture for 2 to 24 hours followed by treatment with dilute hydrochloric acid provides the 1-aryl- and 1-alkyl-substituted Δ^2-tetrazoline-5-ones, respectively [103].

Previously, the synthesis of 1-phenyl-Δ^2-tetrazoline-5-one had been performed by the fusion of potassium tetrazole-5-sulfonate with potassium hydroxide [104] or by the treatment of tetrazole-5-sulfonic acid with a 2N solution of potassium hydroxide [105].

It was shown that isocyanates fail to react with sodium azide alone while hydrazoic acid reacts with isocyanates to the corresponding carbamoyl azides [106]. Nevertheless, different 1,4-disubstituted Δ^2-tetrazoline-5-ones are accessible by 1,3-dipolar cycloaddition of organic azides with suitable isocyanates [107].

Alkyl isocyanates, like *n*-butyl isocyanate, do not react with different alkyl azides and aryl azides respectively. In contrast, aryl isocyanates **131** react with alkyl azides **130** like *n*-butyl azide or cyclohexyl azide to yield 1-alkyl-4-aryl-Δ^2-tetrazoline-5-ones **132**, however, aryl isocyanates do not react with aryl azides. The reactions take place within some hours and up to several days at elevated temperatures, ranging from 55 to 130 °C, and are performed in benzene or without solvent (Scheme 29A). The addition of aryl azides to acyl isocyanates, such as benzoyl isocyanate or carboalkoxy isocyanates like chloroacetyl isocyanate and trichloroacetyl isocyanate, was unsuccessfully attempted at different reaction conditions [107].



Scheme 29 **A** Reaction of alkyl azides **130** with aryl isocyanates **131** to yield 1-alkyl-4-aryl-Δ^2-tetrazoline-5-ones **132** **B** Reaction of alkyl azides **133** with acyl isocyanates or carboalkoxy isocyanates **134** to 1-alkyl-4-acyl-Δ^2-tetrazoline-5-ones and 1-alkyl-4-carboalkoxy-Δ^2-tetrazoline-5-ones **135** (**C**). Reaction of aryl azides and alkyl azides **137** with sulfonyl isocyanates **138** to produce 1-aryl-4-sulfonyl-Δ^2-tetrazoline-5-ones and 1-alkyl-4-sulfonyl-Δ^2-tetrazoline-5-ones **139** [107]

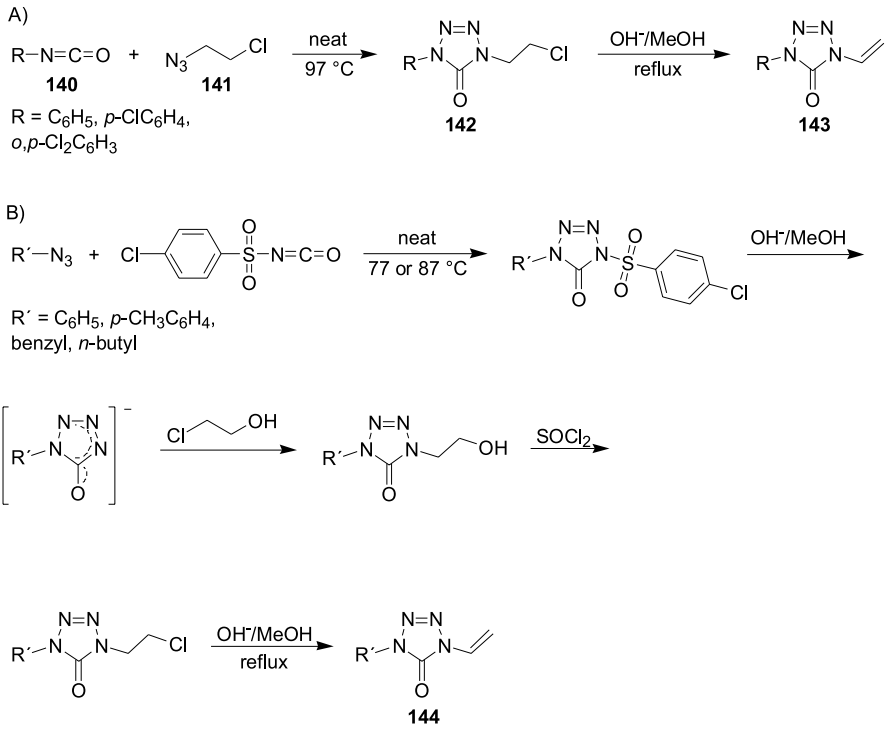
In contrast, the solvent-free, thermal reactions (typically performed at 25 °C, 55 °C or 100 °C) of acyl isocyanates and carboalkoxy isocyanates **134** with alkyl azides **133** lead to the corresponding 1-alkyl-4-acyl-Δ^2-tetrazoline-5-ones and 1-alkyl-4-carboalkoxy-Δ^2-tetrazoline-5-ones **135** in good yields. In general, electron-withdrawing substituents on the used isocyanate were found to increase the yields. The reaction time for this type of reaction ranges from some days up to one month. The 1-alkyl-4-acyl-Δ^2-tetrazoline-5-ones and 1-alkyl-4-carboalkoxy-Δ^2-tetrazoline-5-ones **135** exhibit the properties of azolides, and they readily undergo hydrolysis and alcoholysis at room temperature, giving the corresponding 1-alkyl-Δ^2-tetrazoline-5-ones **136** (Scheme 29B) [107].

Aryl azides and alkyl azides **137** readily react with sulfonyl isocyanates **138** under thermal conditions (typically at 25 °C or 55 °C) in toluene, benzene, carbon tetrachloride or without solvent to give 1-aryl-4-sulfonyl-Δ^2-tetrazoline-5-ones and 1-alkyl-4-sulfonyl-Δ^2-tetrazoline-5-ones **139** respectively in good yields [107, 108]. The reaction time of this reaction ranges from a few minutes to one month (in exceptional cases up to several months), depending on the type of organic azide and the type of sulfonyl isocyanate. This method is also suitable for the synthesis of bis-tetrazolinones, starting from diisocyanates or diazides. Heating of 1-alkyl-4-sulfonyl-Δ^2-tetrazoline-5-ones **139** leads to their thermal decomposition at about 100 °C into starting materials **137** and **138** by cycloreversion (Scheme 29C) [107].

In summary, alkyl azides react with aryl isocyanates, acyl isocyanates, carboalkoxy isocyanates and sulfonyl isocyanates to afford the corresponding 1,4-disubstituted Δ^2-tetrazoline-5-ones. In contrast, the cycloaddition reaction of aryl azides to isocyanates is limited to sulfonyl isocyanates, leading to 1-aryl-4-sulfonyl-Δ^2-tetrazoline-5-ones.

Denecker and co-workers extended the described methods for the different syntheses of 1,4-disubstituted Δ^2-tetrazoline-5-ones to two syntheses of 1-vinyl-4-substituted-Δ^2-tetrazoline-5-ones **143** and **144** [109], avoiding the use of highly explosive vinyl azide [110]. The first method for the synthesis of 1-vinyl-4-substituted-Δ^2-tetrazoline-5-ones **143** is the reaction of aryl isocyanates **140** with an excess of β-chloroethyl azide (**141**), followed by dehydrochlorination of the cycloaddition product **142** with dilute base (Scheme 30A). The main disadvantage of this method is the long reaction time, typically five to six weeks at 97 °C, that is needed to accomplish the first cycloaddition step. Additionally, alkyl isocyanates and aryl isocyanates with electron-donating substituents do not react. The second alternative method for the synthesis of 1-vinyl-4-substituted-Δ^2-tetrazoline-5-ones **144** profits from the activating effect of a sulfonyl group in isocyanate cycloaddition reactions that enables the synthesis of vinyltetrazolinones with alkyl substituents or electron-rich aryl substituents at the 4-position (Scheme 30B).

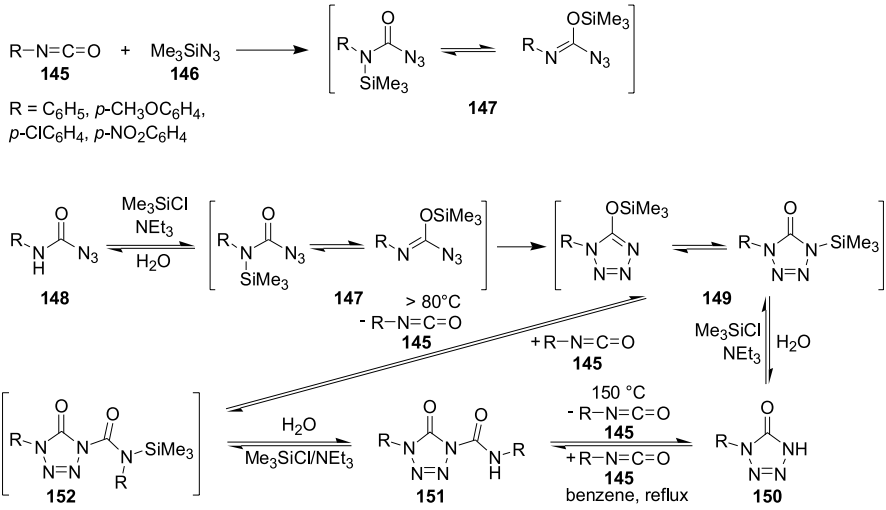
Trimethylsilyl azide (TMSA, **146**), that behaves as a 1,3-dipole like other organic azides, has also been shown to react with isocyanates **145** [111].



Scheme 30 Two different methods for the synthesis of 1-vinyl-4-substituted-Δ^2-tetrazoline-5-ones **143** and **144** [109]

The reaction of phenyl isocyanate (**145**, R = C_6H_5) with TMSA (**146**), followed by desilylation of the product **147** (R = C_6H_5) with water provides phenylcarbamoyl azide (**148**, R = C_6H_5), 1-phenyl-Δ^2-tetrazoline-5-one (**150**, R = C_6H_5) and its phenylcarbamoyl derivative **151** (R = C_6H_5). The appropriately generated products and yields are greatly dependent on the reaction conditions. The reaction of TMSA (**146**) with 1 equivalent of phenyl isocyanate (**145**, R = C_6H_5) in dry benzene at 50–60 °C for 24 hours provides phenylcarbamoyl azide (**148**, R = C_6H_5) in 57% yield, while the same reaction performed without solvent gives phenylcarbamoyl azide (**148**, R = C_6H_5), 1-phenyl-Δ^2-tetrazoline-5-one (**150**, R = C_6H_5) and its phenylcarbamoyl derivative **151** (R = C_6H_5) in 21%, 8% and 28% yield respectively. In contrast, the reaction of 2 equivalents of TMSA (**146**) with phenyl isocyanate as well as with *p*-methoxyphenyl, *p*-chlorophenyl and *p*-nitrophenyl isocyanate **145** without solvent at reflux temperature for 24 hours affords the corresponding 1-aryl-Δ^2-tetrazoline-5-ones **150** in good yields. This method for the preparation of 1-aryl-Δ^2-tetrazoline-5-ones **150** consequently is superior to the earlier described approach [102] in terms of both yields and the simple procedure.

The reaction of the formed 1-aryl-Δ^2-tetrazoline-5-one **150** with the isocyanate **145** in boiling benzene gives the corresponding arylcarbamoyl derivative **151**, whereas on being heated at 150 °C, the arylcarbamoyl derivative **151** reverts into 1-aryl-Δ^2-tetrazoline-5-one **150** and isocyanate **145**. The pathway for the formation of 1-aryl-Δ^2-tetrazoline-5-ones **150** and their arylcarbamoyl derivatives **151** is shown in Scheme 31.

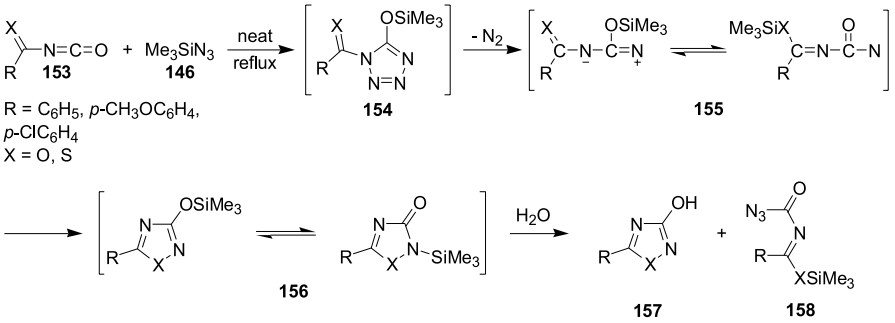


Scheme 31 Formation of 1-aryl-Δ^2-tetrazoline-5-ones **150** and their arylcarbamoyl derivatives **151** from arylisocyanates **145** and TMSA (**146**) [111]

The reaction of TMSA (**146**) with benzoyl isocyanate, *p*-methoxybenzoyl isocyanate or *p*-chlorobenzoyl isocyanate **153** (X=O) for 6 hours without solvent at a reflux temperature and subsequent treatment of the reaction mixture with ethanol provides the corresponding 5-aryl-3-hydroxy-1,2,4-oxadiazoles **157** (X=O) in good yields. This synthesis for 3-hydroxy-5-phenyl-1,2,4-oxadiazole **157** ($R = C_6H_5$, X=O) is an alternative to the formerly described demethylation of 3-methoxy-5-phenyl-1,2,4-oxadiazole, generated from dimethyl-*N*-benzoyliminothiolcarbonate and hydroxylamine [112]. In addition, TMSA (**146**) reacts in the same way with thiobenzoyl, *p*-methoxythiobenzoyl and *p*-chlorothiobenzoyl isocyanate **153** (X=S) to give the corresponding 5-aryl-3-hydroxy-1,2,4-thiadiazoles **157** (X=S) in good yields. Scheme 32 outlines a possible pathway for the formation of these compounds.

Among various heterocyclic scaffolds which display biological activity, the Δ^2-tetrazoline-5-one scaffold is an interesting candidate. Depending on the substitution pattern, Δ^2-tetrazoline-5-ones can serve either as substances for pest management or for medical purposes.

Some Δ^2-tetrazoline-5-ones that are accessible by the reactions discussed above are known for their efficient herbicidal, fungicidal or insecticidal prop-



Scheme 32 Possible pathway for the formation of 5-aryl-3-hydroxy-1,2,4-oxadiazoles **157** (X=O) and 5-aryl-3-hydroxy-1,2,4-thiadiazoles **157** (X=S) respectively, starting from aroylisocyanate **153** (X=O) or thioaroylisocyanate **153** (X=S) and TMSA (**146**) [111]

erties and are therefore interesting molecules for pest management (Fig. 1). Presumably due to the profitable pesticide market, most of the papers dealing with Δ^2-tetrazoline-5-ones as pesticides were published as patents. In particular, 1-aryl-4-carbamoyl-Δ^2-tetrazoline-5-ones were often investigated in this context and were partially found to be potent pesticides [113–121]. One of these candidates is fentrazamide (**160**), a commercially available herbicide with Δ^2-tetrazoline-5-one structure that features a carbamoyl sub-

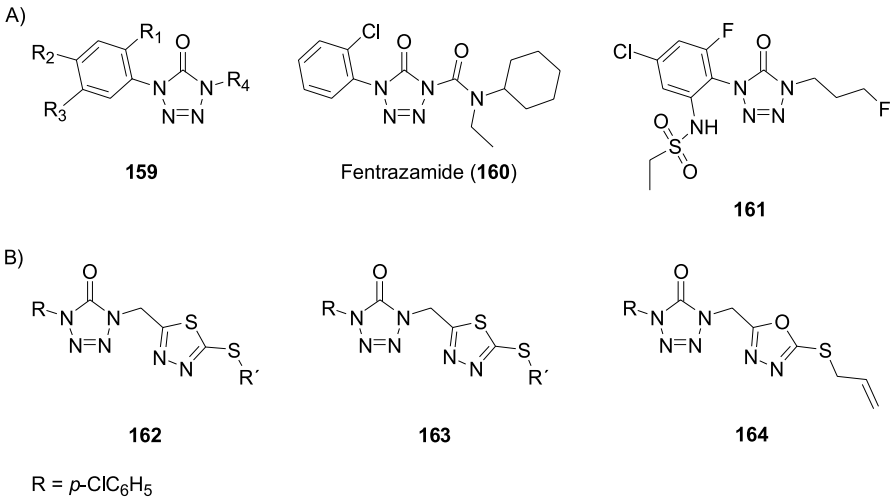
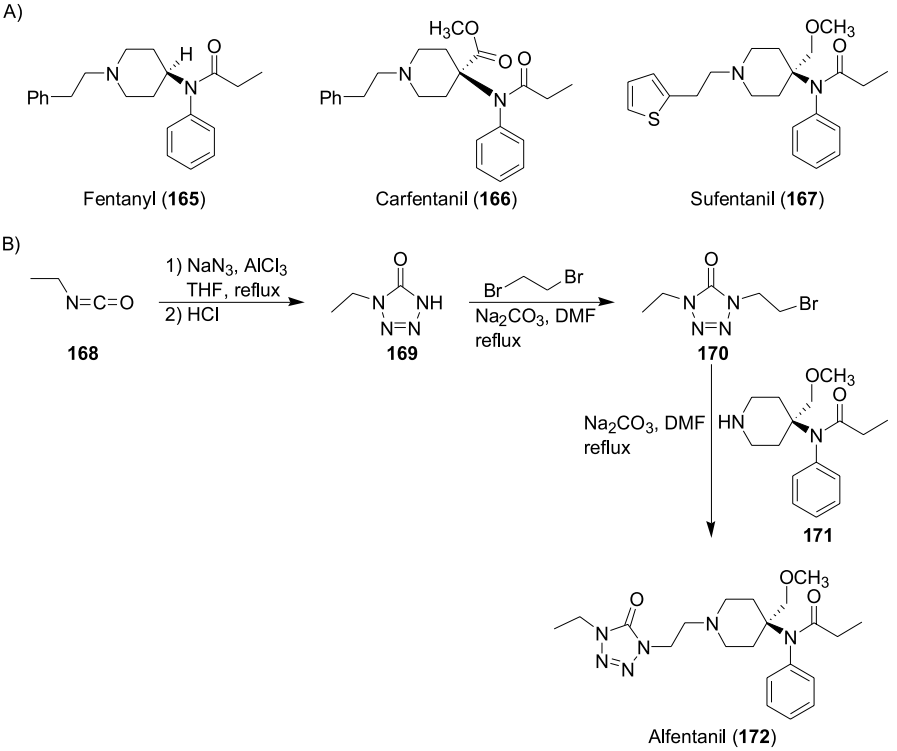


Fig. 1 **A** General structure of herbicidal 1-aryl-4-substituted-Δ^2-tetrazoline-5-ones **159**, structure of fentrazamide (**160**) and 1-aryl-4-(3-fluoropropyl)-Δ^2-tetrazoline-5-one **161**; **B** Δ^2-tetrazoline-5-ones with insecticidal activity: **162** (R′ = CH_2COOEt) and **164** show high insecticidal activity against *T. cinnabarinus*, **163** (R′ = Et) shows insecticidal activity against *A. medicagini* [113–125]

stituent at the 4-position. Fentrazamide is highly effective against many weeds and acts by way of inhibition of cell division [122]. Especially, the substituent in the 4-position of the Δ^2-tetrazoline-5-one scaffold seems to be important for the mode of action since members of a family of 4-(3-fluoropropyl)-substituted Δ^2-tetrazoline-5-ones (e.g., compound **161**) were found to inhibit protoporphyrinogen oxidase, an essential enzyme in chlorophyll synthesis [123, 124]. Besides their biological activity as herbicides and fungicides, Δ^2-tetrazoline-5-ones exhibit insecticidal activity, for example Δ^2-tetrazoline-5-ones with 1,3,4-thiadiazole and 1,3,4-oxadiazole moieties at the 4-position of the Δ^2-tetrazoline-5-one scaffold (**162–164**) [125]. Interestingly, these Δ^2-tetrazoline-5-ones act selectively as insecticides and exhibit no activity against herbicides, suggesting that the substituent in the 4-position seems to be important for the mode of action.

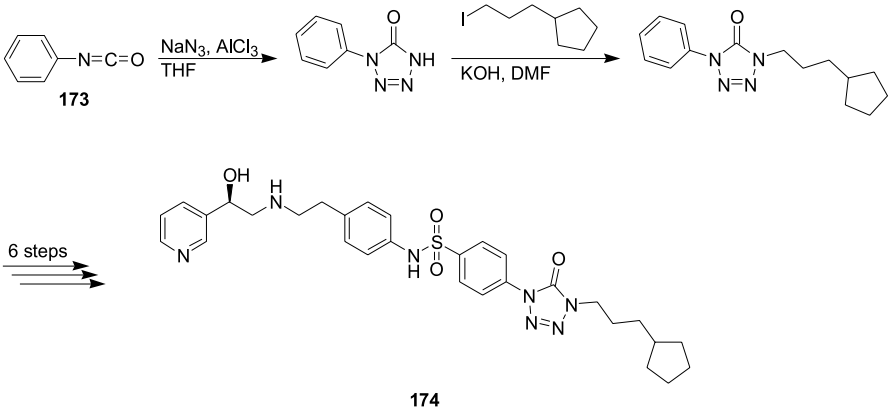
In addition, Δ^2-tetrazoline-5-ones are interesting molecules for medicine in the field of anesthesia and obesity. Fentanyl (**165**), which is a synthetic opioid from the family of anilinopiperidines [126], is a very potent analgesic, though its action is difficult to control. Based on the structure of fentanyl



Scheme 33 **A** Structures of the synthetic opioids fentanyl (**165**), carfentanil (**166**) and sufentanil (**167**), **B** Synthesis of the synthetic opioid alfentanil (**172**) [128]

(**165**), different structure activity investigations were performed that provided some long acting, better controllable and very potent derivatives of fentanyl (**165**), like carfentanil (**166**) and sufentanil (**167**) (Scheme 33A) [127]. The synthesis and structure activity investigation of a series of different 4-piperidine substituted 1,4-disubstituted Δ^2-tetrazoline-5-ones, with a piperidine scaffold similar to that of fentanyl (**165**), led to the discovery of alfentanil (**172**) [128]. Alfentanil (**172**) is a commercially available, well controllable synthetic opioid, distributed as Alfenta® and Rapifen®, that is mainly used for short time anesthesia in medicine, for example during curettage or reposition. The initial step for the synthesis of these fentanyl derivatives with tetrazoline-5-one scaffold is the reaction of an alkyl isocyanate (e.g., **168**) or acid chloride with aluminum azide, generated from sodium azide and aluminum chloride, in tetrahydrofuran at reflux temperature to give the corresponding 1-substituted Δ^2-tetrazoline-5-one (e.g., **169**) [101] that is subject to 4-alkylation in the next step, followed by attachment of the appropriate piperidine moiety (e.g., **171**) to give the 1,4-disubstituted Δ^2-tetrazoline-5-one (e.g., alfentanil (**172**)) (Scheme 33B) [128].

Obesity affects approximately 30% of the adult population and is closely associated with the development of type II diabetes, coronary artery diseases and hypertension. One possibility to circumvent these diseases is weight reduction. Together with decreased food intake, agonists of the β_3 adrenergic receptor are interesting compounds to treat obesity and are therefore attractive targets for drug development. The stimulation of β_3 adrenergic receptors at the surface of adipocytes causes lipolysis, leading to activation and upregulation of the uncoupling protein UCP1. This results in a net increase in energy utilization. A series of β_3 adrenergic receptor agonists from the class of imidazolidinones or imidazolones were developed, but displayed poor oral bioavailability due to oxidation of the ring carbon atoms [129, 130]. Consequently, the heterocyclic ring of these compounds was replaced by

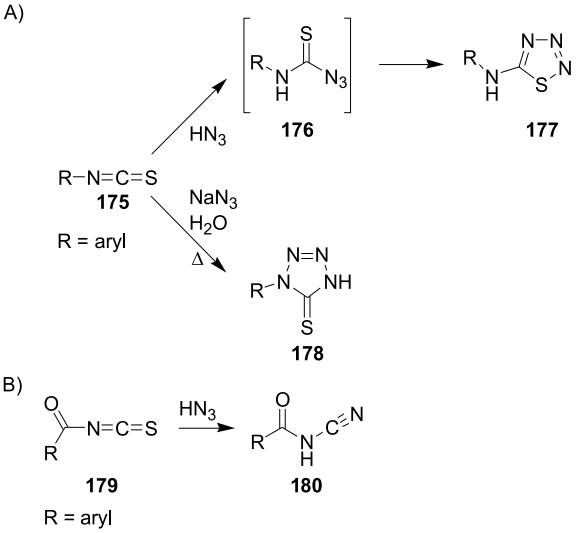


Scheme 34 Synthesis of β_3 adrenergic receptor L-770644 (**174**) [131]

a Δ^2-tetrazoline-5-one scaffold [131]. The first step in the synthesis of these Δ^2-tetrazoline-5-one containing compounds is the preparation of the Δ^2-tetrazoline-5-one ring, starting from phenyl isocyanate (**173**) and aluminum azide [102]. The study afforded a potent and selective agonist of the human β_3 adrenergic receptor, L-770644 (**174**), with good oral bioavailability in animal experiments (Scheme 34) [131].

4.2 Addition of Azides to Isothiocyanates

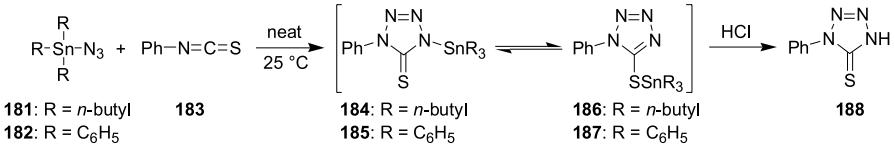
The reactivity of electrophilic isothiocyanates towards inorganic and organic azides is well known. The conversion of hydrazoic acid with aryl isothiocyanates **175** provides 5-amino-substituted 1,2,3,4-thiatriazoles **177** by addition of hydrazoic acid to the C=S bond of the isothiocyanate moiety, probably via unstable thiocarbamoyl azides **176** [132]. Benzoyl isothiocyanate (**179**, $R = C_6H_5$), for example, reacts with hydrazoic acid to benzoylcyanamide (**180**, $R = C_6H_5$). In contrast, the reaction of sodium azide with isothiocyanates **175** occurs at the C=N bond of the isothiocyanate moiety and gives 1-substituted-Δ^2-tetrazoline-5-thiones, also known as 1-substituted-5-mercaptotetrazoles **178** (Scheme 35) [133–135].



Scheme 35 **A** Reaction of aryl isothiocyanates **175** with hydrazoic acid or sodium azide, **B** Reaction of aroyl isothiocyanates **179** with hydrazoic acid [132–135]

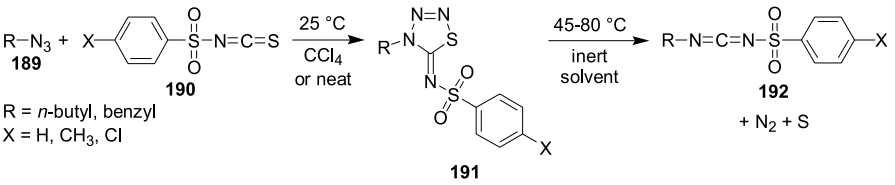
The reaction of diisothiocyanates with sodium azide in water at reflux temperature within 4 hours provides bis(tetrazoline-5-thiones) as difunctional compounds [136]. If organotin azides like tri-*n*-butyltin azide (**181**) or triph-

enyltin azide (**182**) are treated with phenyl isothiocyanate (**183**), the corresponding 1-phenyl-4-tri-*n*-butyltin-Δ^2-tetrazoline-5-thione (**184**) or 1-phenyl-4-triphenyltin-Δ^2-tetrazoline-5-thione (**185**), respectively, is formed. Upon treatment with cold dilute hydrochloric acid, these compounds are converted to 1-phenyl-Δ^2-tetrazoline-5-thione (**188**) (Scheme 36) [137]. It was shown by structural analyses that organic tin azides undergo [3+2]-cycloaddition with organic isothiocyanates at the C=N functionality. Furthermore, the formed products exist rather in the thiol form than in the thione form, as published earlier [137], and display the tin atom at the sulfur [138]. In general, organometallic azides add to the C=N functionality of isothiocyanates.



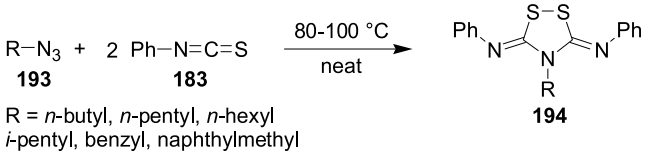
Scheme 36 The reaction of organotin azides **181** and **182** with phenyl isothiocyanate (**183**) gives 1-phenyl-4-organotin-Δ^2-tetrazoline-5-thiones **184** and **185** and their tautomers (*S*-organotin)-1-phenyl-5-thiotetrazoles **186** and **187**. The latter are the confirmed structures of the formed intermediates that upon treatment with dilute hydrochloric acid, provide 1-phenyl-Δ^2-tetrazoline-5-thione (**188**) [137, 138]

Organic azides like alkyl azides and TMSA (**146**) are also able to add to isothiocyanates. Alkyl azides **189**, namely *n*-butyl azide or benzyl azide, react with an equimolar amount of arylsulfonyl isothiocyanates **190** at room temperature in carbon tetrachloride or without solvent during 7 hours up to 2 days to exclusively afford 4-alkyl-5-arylsulfonylimino-1,2,3,4-thiatriazolines **191** in 50–75% yield. The product was the result of a [3+2]-cycloaddition to the C=S bond of the isothiocyanate moiety. Upon heating to 45–80 °C in inert solvents, the 4-alkyl-5-arylsulfonylimino-1,2,3,4-thiatriazolines **191** evolve nitrogen and sulfur, decomposing to sulfonylcarbodiimides **192** which are valuable precursors for the synthesis of further heterocycles like 4-aminothiazolidines or thiazolines (Scheme 37) [139, 140].



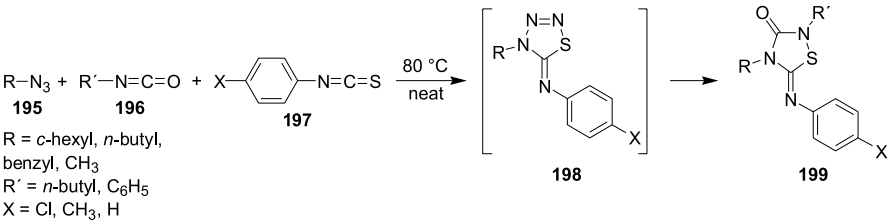
Scheme 37 Reaction of alkyl azides **189** with arylsulfonyl isothiocyanates **190** to yield 4-alkyl-5-arylsulfonylimino-1,2,3,4-thiatriazolines **191**. Thermal decomposition of the latter results in the formation of sulfonylcarbodiimides **192** [139, 140]

The reaction of phenyl isothiocyanate (**183**) with primary alkyl azides **193** in a 2:1 ratio at 80–100 °C without solvent provides access to 4-alkyl-3,5-bis-(phenylimino)-1,2,4-dithiazolidines **194** in 29–65% yield (Scheme 38) [141].



Scheme 38 Reaction of alkyl azides **193** with 2 equivalents of phenyl isothiocyanate (**183**) to 4-alkyl-3,5-bis-(phenylimino)-1,2,4-dithiazolidines **194** [141]

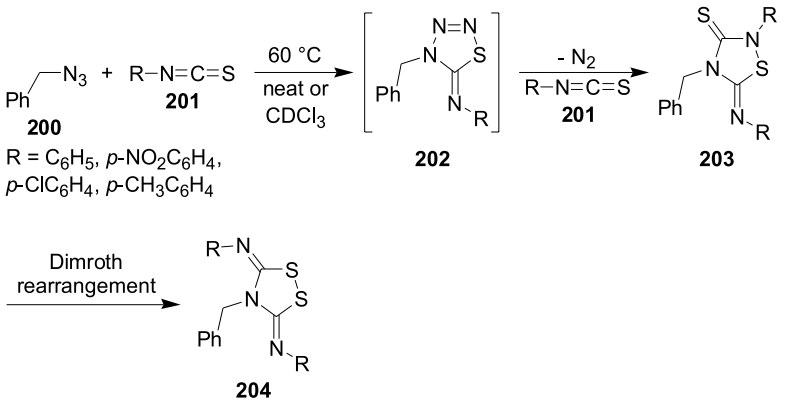
Furthermore, isothiocyanates can be used for the three component synthesis of 5-imino-1,2,4-thiadiazolidine-3-ones **199** (Scheme 39). This type of heterocycle is accessible in high yields by heating alkyl azides **195** and alkyl or aryl isocyanates **196** at 80 °C for 7 days with subsequent addition of aryl isothiocyanates **197** to the reaction mixture within this time. The reaction seems to proceed *via* an initial iminothiatriazoline **198** that readily forms the 5-imino-1,2,4-thiadiazolidine-3-ones **199** by reaction with isocyanates **196** [142].



Scheme 39 Three component synthesis of 5-imino-1,2,4-thiadiazolidine-3-ones **199** from alkyl azides **195**, alkyl or aryl isocyanates **196** and aryl isothiocyanates **197** [142]

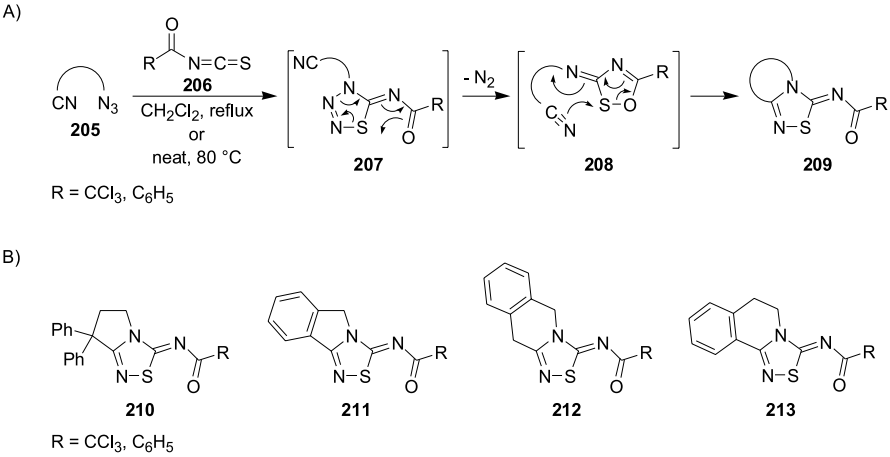
The reaction of benzyl azide (**200**) with 2 equivalents of an aryl isothiocyanate **201** at 60 °C for some days provides a mixture of five types of different products. The main component in the beginning of the reaction is a thiadiazolidine **203** that undergoes isomerization to a dithiazolidine **204** by Dimroth rearrangement at the end of the reaction (Scheme 40). Mechanistically, alkyl azides cycloadd preferentially to the C=S bond of aryl isothiocyanates to give the corresponding mono adduct **202** as an intermediate. Further addition of another isothiocyanate **201** to the formed 4-alkyl-5-aryl-imino-1,2,3,4-thiatriazolines **202** and loss of nitrogen readily leads to the formation of the thiadiazolidine **203** and dithiazolidine **204** after Dimroth rearrangement, respectively [143].

Organic alkyl azides **205** that bear a nitrile function at the γ- or δ-position react with one equivalent of an acyl isothiocyanate **206** in a domino



Scheme 40 Reaction of benzyl azide (**200**) with 2 equivalents of an aryl isothiocyanate **201** yields a thiadiazolidine **203** in the early stage of the reaction, and after Dimroth rearrangement of the latter, subsequently a more stable dithiazolidine **204** is formed [143]

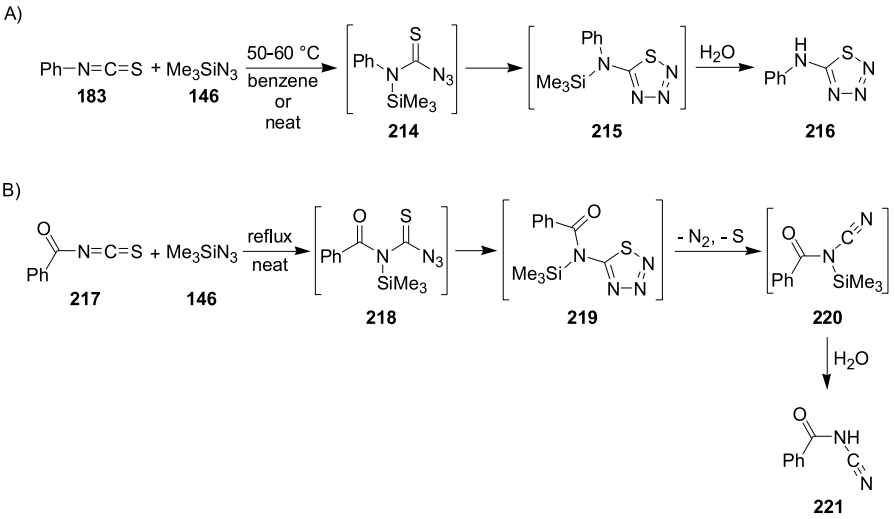
reaction to give a fused dihydro-1,2,4-thiadiazolimine **209.** From a mechanistic point of view, the azide **205** cycloadds in the first step of the reaction to the C=S function of the isothiocyanate **206** and gives an unstable dihydrothiatriazole **207** that decomposes by anchimeric assistance of the carbonyl function to produce nitrogen and a 1,2,4-oxathiazol-3-imine **208.** The latter possesses a reactive thioimidate structural unit and undergoes an intramolecular cycloaddition-ring-opening reaction, providing the fused dihydro-1,2,4-thiadiazolimine **209.** The reaction is typically performed in



Scheme 41 **A** Reaction mechanism for the generation of fused dihydro-1,2,4-thiadiazolimines **209, B** Some dihydro-1,2,4-thiadiazolimines (**210–213**) that have been synthesized from an appropriate cyano-substituted azide and an acyl isothiocyanate [144]

dichloromethane at reflux temperature or without solvent at 80 °C, depending on the used isocyanate. Reaction times range from 16 hours to two days (Scheme 41) [144].

As discussed in the previous section, TMSA (**146**) reacts with aryl, aroyl and thioaroyl isocyanates. Consequently, the behavior of aryl isothiocyanates and aroyl isothiocyanates with TMSA (**146**) was also investigated, however the reactivity of TMSA (**146**) towards both types of isothiocyanates was very low. The reaction of phenyl isothiocyanate (**183**) with TMSA (**146**) in benzene or without solvent at 50–60 °C for 24 or 40 hours, followed by desilylation with water, provided the appropriate 1,2,3,4-thiatriazole **216** in only 1.6% and 3.4% yield respectively, together with recovery of starting material. On the other hand, the reaction of benzoylisothiocyanate (**217**) with TMSA (**146**) without solvent under reflux for 5 hours gave a cyanamide **221** in 23% yield and a small amount of sulfur, accompanied by recovery of starting material. In both cases, the reaction proceeds via initial formation of a silylated azide **214** or **218**, followed by cyclization of the azido group to a thiocarbonyl group to give silylated 1,2,3,4-thiatriazole **215** or **219**. Forcing reaction conditions using benzoyl isothiocyanate (**217**) as starting material gives silylated cyanamide **220** with the elimination of both nitrogen and sulfur. Desilylation of silylated 1,2,3,4-thiatriazole **215** (Scheme 42A) or cyanamide **220** (Scheme 42B) provides 1,2,3,4-thiatriazole **216** and cyanamide **221**, respectively [111].

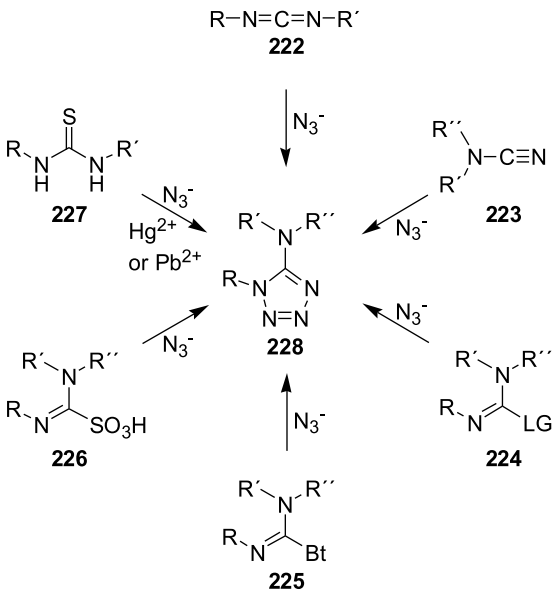


Scheme 42 **A** Reaction of phenyl isothiocyanate (**183**) with TMSA (**146**), followed by desilylation, gives a 1,2,3,4-thiatriazole **216**, **B** Reaction of benzoyl isothiocyanate (**183**) with TMSA (**146**), followed by desilylation, yields a cyanamide **221** [111]

4.3
Synthesis of Substituted 5-Aminotetrazoles Using Azides

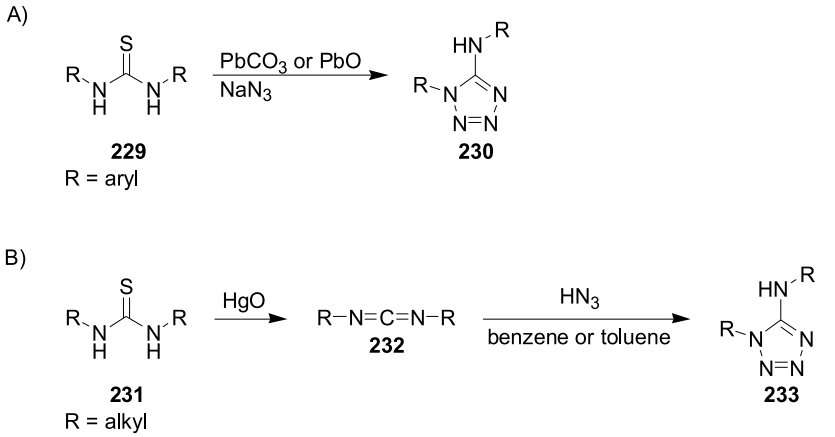
Tetrazoles are a promising class of heterocyclic compounds since they exhibit a wide scope of biological activity. In particular, 5-aminotetrazoles are interesting substances as they feature anti-allergic and anti-asthmatic [145–149], antiviral and anti-inflammatory [150], anti-neoplastic [151, 152] and cognition disorder activities [153]. In addition, activity as cholecystokinin (CCK) antagonists [154] and as antibiotics against a range of bacteria [155] has been observed.

The syntheses of substituted 5-aminotetrazoles **228**, using azide ions for assembling the tetrazole scaffold, can be divided into two different approaches. The first approach is the addition of sodium azide to carbodiimides **222** [156, 157] or cyanamides **223** [158–161]. The second approach is the nucleophilic substitution of a chlorine in α-chloroformamidines **224** [162], the nucleophilic substitution of benzotriazole in (benzotriazolyl)carboximidamides **225** [163], the nucleophilic substitution of the sulfite anion in aminoiminomethanesulfonic acids **226** [164] and the nucleophilic substitution of sulfur from thioureas **227** in the presence of mercury [165] or lead [166–169] salts in the presence of an azide ion (Scheme 43). In this chapter, the main focus is on the addition of azides to carbodiimides **222** to form substituted 5-aminotetrazoles **228**.



Scheme 43 Methods for the synthesis of substituted 5-aminotetrazoles **228** that involve azides [156–169]

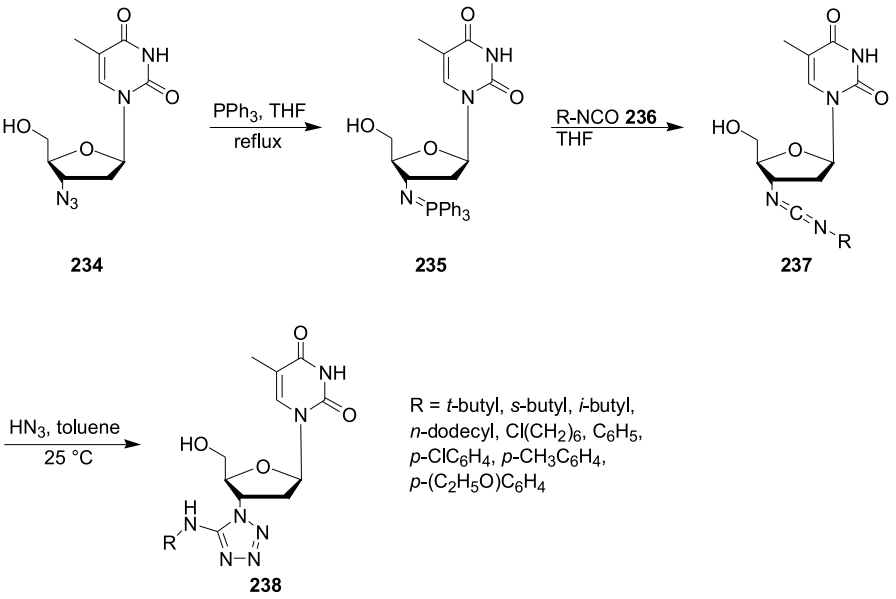
The synthesis of symmetric 1-aryl 5-arylaminotetrazoles **230** was initially performed by reacting symmetrical diarylthioureas **229** with sodium azide in the presence of lead carbonate or lead oxide. The reaction proceeds *via* the transitional formation of a diarylcarbodiimide that readily reacts with the azide ion to give the 1-aryl-5-arylaminotetrazole **230** (Scheme 44A) [166–168]. Percival and co-workers extended this method to the synthesis of a group of symmetrical 1-alkyl-5-alkylaminotetrazoles **233** that were prepared from the appropriate symmetric carbodiimides **232** in benzene or toluene with hydrazoic acid (Scheme 44B) [156]. The carbodiimides **232** were generated in a previous step from symmetrical dialkylthioureas **231** in the presence of mercuric oxide.



Scheme 44 **A** Conversion of diarylthioureas **229** to 1-aryl-5-arylaminotetrazoles **230** [166–168], **B** Reaction of dialkylthioureas **231** or dialkylcarbodiimides **232** to 1-alkyl-5-alkylaminotetrazoles **233** [156]

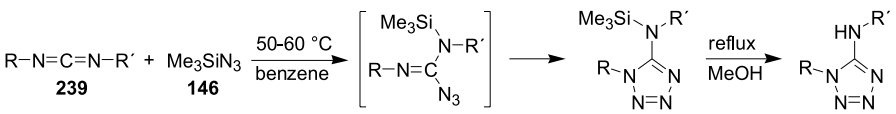
The addition of hydrazoic acid to a carbodiimide [156] was used by Häbich in the synthesis of analogues **238** of 3′-azido-3′-deoxythymidine (AZT, **234**). AZT (**234**) is an important drug for the treatment of AIDS that belongs to the class of nucleoside reverse transcriptase inhibitors. AZT (**234**) was transformed to the carbodiimide **237** through Staudinger reaction with triphenylphosphane, followed by reaction of **235** with an alkyl or aryl isocyanate **236**. The carbodiimide **237** was then treated with hydrazoic acid in toluene at room temperature for 6 hours to give the desired 5-aminotetrazole **238** in 43–90% yield (Scheme 45) [170].

An extension of these methods that employs hydrazoic acid as an azide donating agent was developed by Tsuge and co-workers. They used TMSA (**146**) and allowed it to react with symmetrical *N*,*N*′-diphenylcarbodiimide or *N*,*N*′-dialkyl carbodiimides **239** in dry benzene at 50–60 °C for 48 hours. The products of these conversions were 1-phenyl-5-[*N*-(trimethylsilyl)-anilino]-



Scheme 45 Synthesis of 3′-azido-3′-deoxythymidine (AZT) analogues **238** as nucleoside reverse transcriptase inhibitors [170]

tetrazole and 1-alkyl-5-[*N*-(trimethylsilyl)-anilino]-tetrazoles **241**, respectively. Desilylation of the silylated tetrazoles **241** with methanol led to 1-phenyl-5-phenylaminotetrazole or 1-alkyl-5-alkylaminotetrazoles **242**. The application of a non-symmetrical carbodiimide did not provide two isomeric tetrazoles as expected, but only one tetrazole in low yield. Consequently, the reaction of *N*-cyclohexyl-*N*′-phenyl carbodiimide (**239**, R = C_6H_5, R′=*c*-hexyl) or *N*-(*n*-butyl)-*N*′-phenyl carbodiimide (**239**, R = C_6H_5, R′=*n*-butyl) with TMSA (**146**) gave 5-(cyclohexylamino)-1-phenyl-tetrazole (**242**, R = C_6H_5, R′=*c*-hexyl) and 5-(*n*-butylamino)-1-phenyl-tetrazole (**242**, R = C_6H_5, R′=*n*-butyl) respectively. Mechanistically, TMSA (**146**) adds to the carbodiimide **239**

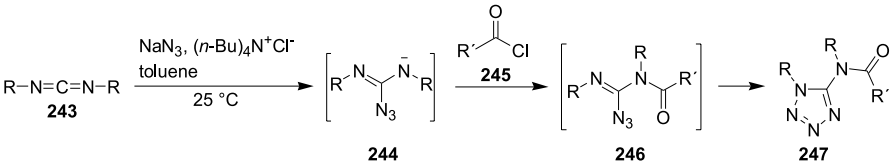


a) R = R′ = C_6H_5
b) R = R′ = *c*-hexyl
c) R = R′ = *i*-propyl
d) R = C_6H_5, R′ = *c*-hexyl
e) R = C_6H_5, R′ = *n*-butyl

Scheme 46 Synthesis of 5-aminotetrazoles **242** starting from symmetrical or non-symmetrical carbodiimides **239** and TMSA (**146**) [111]

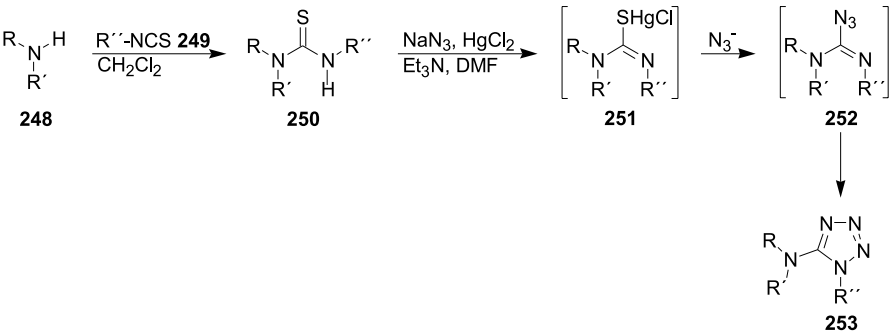
and a silylated guanyl azide **240** is formed in which the trimethylsilyl group is attached to the more basic nitrogen atom. Subsequent cyclization of this guanyl azide **240** to silylated 5-aminotetrazole **241**, followed by desilylation, gives the final 5-aminotetrazole **242** (Scheme 46) [111].

A one-pot protocol for the synthesis of 1-aryl-5-(*N*-aryl-*N*-aroylamino)-tetrazoles **247** from symmetrical diaryl carbodiimides **243** with sodium azide under phase transfer conditions in toluene at room temperature was developed by Ding and Weber. The carbodiimide **243** reacts with sodium azide to form a guanyl azide **244** which, after reaction with an aroyl chloride **245,** undergoes electrocyclization to yield the substituted tetrazole **247** (Scheme 47). The reaction is limited to symmetrical diaryl carbodiimides. Dialkyl carbodiimides fail to react under these conditions while asymmetrical diaryl carbodiimides lead to a mixture of tetrazole isomers [157].



Scheme 47 Synthesis of 1-aryl-5-(*N*-aryl-*N*-aroylamino)-tetrazoles **247** from symmetrical diaryl carbodiimides **243** using phase transfer conditions [157]

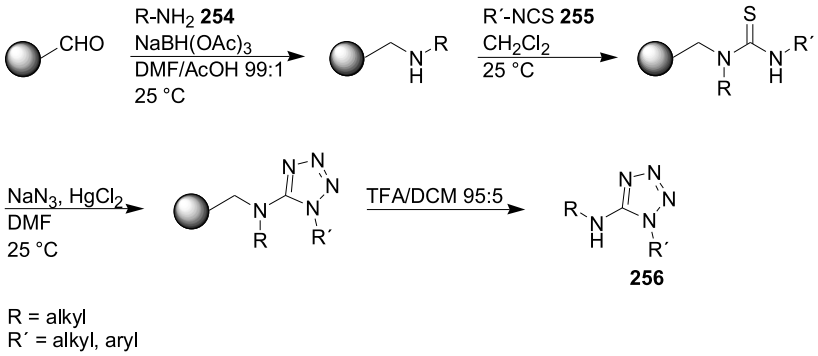
A useful method for the preparation of mono-, di- and trisubstituted 5-aminotetrazoles **253** starts from substituted thiourea **250** that is readily accessible by conversion of an amine **248** with an isothiocyanate **249.** The thiourea **250** is reacted at room temperature with sodium azide in the presence of mercuric chloride in DMF with triethylamine as a base. In the initial step of the reaction, a mercury(II)-activated thiourea **251** is formed as an



Scheme 48 Synthesis of mono-, di- and trisubstituted 5-aminotetrazoles **253** [165]

intermediate that is subject to an attack of the azide ion and results in the generation of an intermediate guanyl azide **252**. Finally, electrocyclization of the latter provides the appropriate 5-aminotetrazole **253** (Scheme 48). By using this method, substituted 5-aminotetrazoles can be synthesized that are not accessible by the reaction of carbodiimides with hydrazoic acid or sodium azide [165].

In order to generate combinatorial libraries of 5-aminotetrazoles, a solid-phase synthesis of these compounds was developed using the findings from the research discussed above. The parallel solid-phase synthesis of 16 disubstituted 5-aminotetrazoles **256** was carried out on the solid-phase using the "teabag" methodology starting from readily available amines **254** and isothiocyanates **255** as building blocks (Scheme 49) [171].



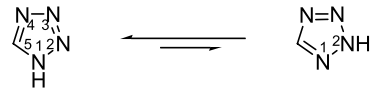
Scheme 49 Solid-phase synthesis of 5-aminotetrazoles **256** [171]

5
Cycloaddition Reactions to X–Y Triple Bonds

The cycloaddition to X–Y triple bonds mainly deals with reactions of azides **258** with nitriles **257** to afford tetrazoles **259**. The general reaction is shown in Scheme 50.

Two tautomeric forms, 1*H*-tetrazole (**260**) and 2*H*-tetrazole (**261**) are possible, for which 1*H*-tetrazole (**260**) is the more important tautomer (Scheme 51).

Scheme 50 General [2+3]-cycloaddition reaction of azides **258** and nitriles **257** towards tetrazoles **259** [1]



1*H*-tetrazole (**260**) 2*H*-tetrazole (**261**)

Scheme 51 Two tautomeric forms of tetrazoles. The balance is on the side of the 1*H*-tetrazole (**260**) [1]

Tetrazoles are interesting functionalities with versatile applications, such as for lipophilic spacers [172], in explosives [173, 174] and as precursors to several nitrogen-containing heterocycles [175, 176]. Beside nitriles, isonitriles (= isocyanides) can act as dipolarophiles in cycloaddition reactions with azides. Those reactions lead to 1-substituted tetrazoles and are described as well. 1-Substituted tetrazoles have also received much attention because of their wide utility [177–179].

Generally, the cycloaddition reaction of azides with X–Y triple bonds can be carried out either under thermal conditions or can be accelerated by catalysis.

5.1 Thermal (Uncatalyzed) Reactions

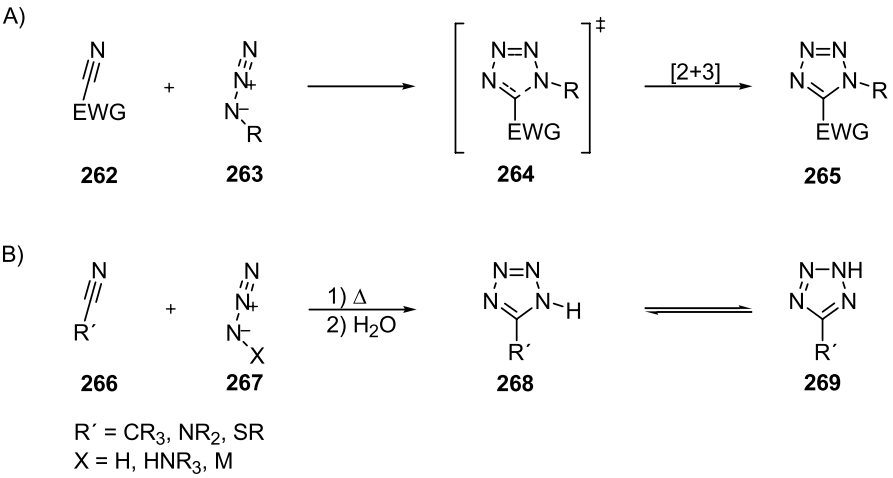
The thermally activated cycloaddition to nitriles was originally performed by heating the reaction mixture to about 100 °C. However, more recent publications also describe cycloaddition reactions without catalyst which proceed in a microwave reactor.

The formation of tetrazoles can generally occur intermolecularly as well as intramolecularly, whereas the latter show enhanced cycloaddition rates and less heating is required.

5.1.1 Intermolecular Cycloaddition Reactions with Azides

During the intermolecular cycloaddition reaction of nitriles with azides, two different mechanisms can be considered, thereby leading to different products. Depending on the nature of the azide, the reaction kinetics differ [172]. Sharpless et al. investigated the kinetics of the reaction and found that it depends on the structure of the azide. If organic azides **263** are used as dipoles, the reaction proceeds via a [2+3]-cycloaddition mechanism, regioselectively giving the 1-alkylated product **265** (Scheme 52A) [180]. In this case, only certain highly activated nitriles **262** can be used [181–185].

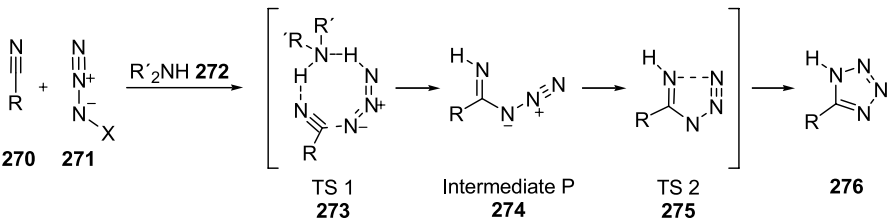
In contrast, azide salts **267** react with nitriles **266** in solution by simple heating through an anionic two-step mechanism leading to 1*H*-tetrazoles **268** (Scheme 52B). The products can be isolated in high yields and the scope of usable nitriles **266** is broad, in contrast to the reaction with organic azides [172].



Scheme 52 Mechanisms of organic azides **263** (**A**) and azide salts **267** (**B**) respectively with nitriles to give tetrazoles **265** and **269** [172]

The formation of tetrazoles from nitriles and azides was investigated regarding the scope and reaction kinetics. As a model, the reaction of HN_3 with nitriles was studied. It was found that the product can be formed in two ways. The first possibility is a direct concerted attack of HN_3 on the nitrile in which the proton is transferred to the nitrile nitrogen with simultaneous formation of the N–C bond. This reaction, in which a protonated azide is implicated, has an activation barrier of around 125 kJ/mol, which displays a high activation barrier and can compete with the neutral and anionic concerted [2+3] cycloadditions, though only for highly inactive nitriles.

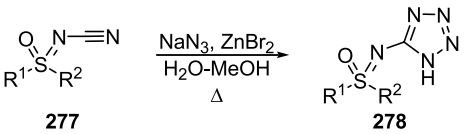
In the second mechanism, the proton stems from an ammonium azide. Compared to the previous model, the activation barriers are almost identical. The calculations showed that in reactions where a proton is available, a stepwise reaction through intermediate P **274** (Scheme 53) is more favorable than [2+3] cycloaddition reactions, either neutral or anionic.



Scheme 53 Supposed mechanism for the reaction between nitriles **270** and azides **271**. Calculations showed, that in presence of a proton, the reaction proceeds via the protonated intermediate P **274** [172]

In this mechanism, the key to the low energy transition state (TS) is the activation of the nitrile by a proton, which is provided by the ammonium salt but can be replaced by other proton sources [172].

An application of such an intermolecular reaction between azides and nitriles was performed by Bolm et al. [186]. They showed the conversion of *N*-cyano sulfoximines **277** to *N*-(1*H*)-tetrazole sulfoximines **278** by addition of sodium azide to the starting material in the presence of $ZnBr_2$.



277 **278**

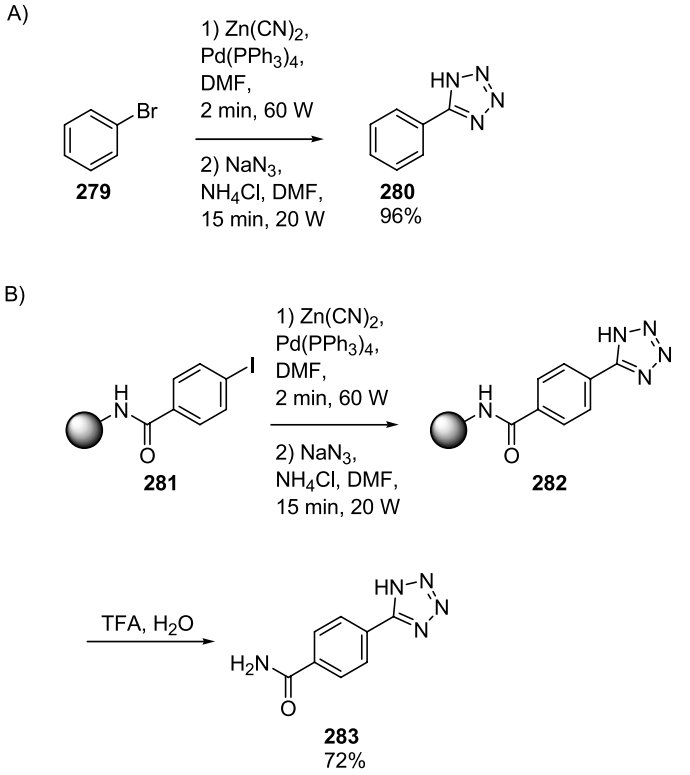
Scheme 54 Conversion of *N*-cyano sulfoximines **277** into *N*-(1*H*)-tetrazole sulfoximines **278** [120]

The reactions occurred in yields of 65–90%. Furthermore, the reaction was carried out with inexpensive and nontoxic zinc bromide and was stereospecific. Thus, easy access to novel enantiopure sulfoximines **278** from the corresponding optically active *N*-cyano derivatives **277** was provided.

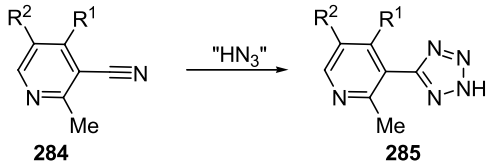
The formation of tetrazoles can also be performed in a one-pot reaction, starting from halides.

The transformation of aryl bromides to tetrazoles via the corresponding cyanides needs long reaction times for completion, often days when electron-rich aryl nitriles are employed [187–191]. Alterman and Hallberg reported that flash heating by microwave irradiation allows the formation of tetrazoles, either in solution or on solid supports, in minutes rather than in hours or days [192]. Several nitriles were converted into tetrazoles by treatment with sodium azide and ammonium chloride in DMF. A microwave power of 20 W was applied to avoid formation of side products. A temperature of 220 °C was reached after 10 min and the reaction time was varied from 10 to 25 min. The yields were generally good and comparable to those reported without microwave irradiation. The tetrazoles could be synthesized starting from the halides by convenient one-pot procedures which delivered very high to quantitative yields (Scheme 55A). The microwave-promoted heating technique is also suitable for conversions of iodides to tetrazoles on solid supports (Scheme 55B). The solid phase reaction was carried out with a Rink linker on Tentagel, and only a negligible decomposition of the solid support had occurred.

Another microwave-assisted tetrazole synthesis was described by Lukyanov et al. They found that the synthesis of sterically-hindered 3-(5-tetrazolyl)pyridines, which showed different biological activities, were not readily accessible by using standard reaction conditions (Scheme 56: conditions c, 105 °C, 72 h) [193].



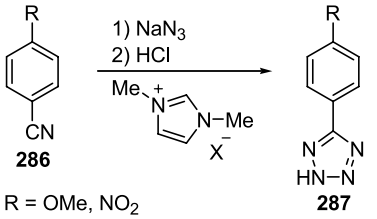
Scheme 55 Conversion of aryl halides into the corresponding tetrazoles via cyanides. **A** Reaction in solution phase and under microwave irradiation. **B** Reaction on solid support with similar reaction conditions to **A**

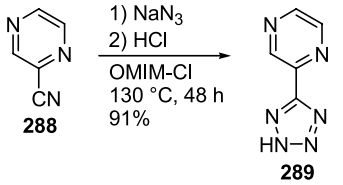


Scheme 56 Synthesis of 3-(5-tetrazolyl)pyridines **285** from nicotino-nitriles **284**. HN_3 = a NaN_3, AcOH, *n*-BuOH; b NaN_3, $ZnBr_2$, H_2O; c Me_3SiN_3, Bu_2SnO, dioxane (also microwave assisted) [193]

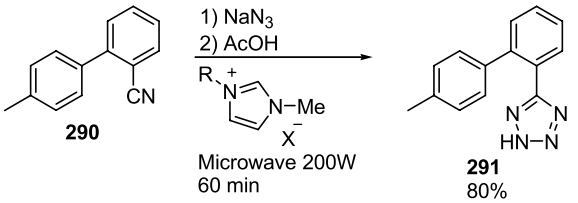
Those hindered pyridines could be successfully prepared using microwave irradiation as an energy source. Reaction conditions (Scheme 56c) gave the best results with the optimal molar ratio being nitrile/Bu_2SnO/Me_3SiN_3 = 1:3:4. All experiments were carried out at 140 °C for 8 h. This shows that microwave irradiation may assist the conversion of sterically-hindered nitriles into tetrazoles that are difficult to achieve by other means.

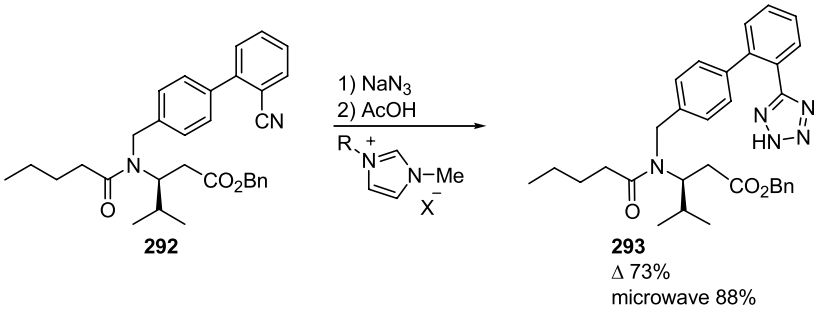
As described in the next sections, the [2+3]-cycloaddition of nitriles and azides is a reliable method for intramolecular reactions (Scheme 59), but volatile azides create tremendous hazards in intermolecular reactions. For large-scale processes, tin azides [194, 195] may be used, however this leads to the problem of recovering the metal salts. The utilization of zinc catalysts





Scheme 57 Tetrazole formation from commercial nitriles, carried out in ionic liquids (OMIM-Cl = 1-octyl-3-methylimidazolium chloride) [198]





Scheme 58 Microwave assisted synthesis of sartane intermediates [199–201]

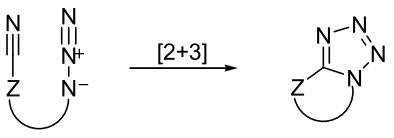
in aqueous solution [224, 225] is an improvement of previous methods, but sometimes requires the tedious removal of zinc salts from acidic products. The solvent free conversion of trimethylsilyl azide with tetrabutylammonium fluoride (TBAF) (Scheme 65) [226] works well for small-scale experiments, but exothermic azide formation will be difficult to control in a large-scale process [196, 197]. Kieser et al. reported safe solvents featuring low vapor pressure and good solubility of NaN_3 in cycloaddition reactions by using ionic liquids, based on alkylated imidazoles, combined with microwave heating (Scheme 57) [198].

It was found that the counter ions of the ionic liquids have a high impact on the isolated yields and that halides are by far better than triflates. Two intermediates from the synthesis of sartane drugs [199–201] were selected to explore the influence of microwave heating.

The reaction time could be dramatically shortened and the reaction was more selective (Scheme 58).

5.1.2 Intramolecular Cycloaddition Reactions with Azides

The rate of cycloaddition reactions of azides and nitriles can be greatly enhanced when the azide and the nitrile moieties are part of the same molecule. Some groups have reported the synthesis of polycyclic tetrazoles via intramolecular cycloaddition reactions, whereby the nitrile is attached to a carbon atom (Scheme 59, $Z = CR_2$) [202–207].

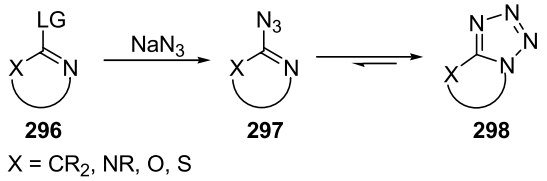


294 **295**

Scheme 59 Synthesis of polycyclic-fused tetrazoles **295** via intramolecular [2+3]-cycloaddition for Z=C [202–207] and Z=O, S, NR [208]

Sharpless et al. showed that nitriles, which are attached to heteroatoms react with sodium azide to form the corresponding 1*H*-tetrazoles at lower temperatures than carbon-bound nitriles (Scheme 59, Z = O, S, NR) [208]. The range of the azidonitrile moiety is broad so the formed tetrazoles can be fused to five- or six-membered rings which can be saturated or unsaturated, and the heteroatom can be an oxygen, nitrogen or a sulfur. The reaction pathway involves imidoyl azide **297**, which spontaneously cyclizes to the tetrazole **298** (Scheme 60).

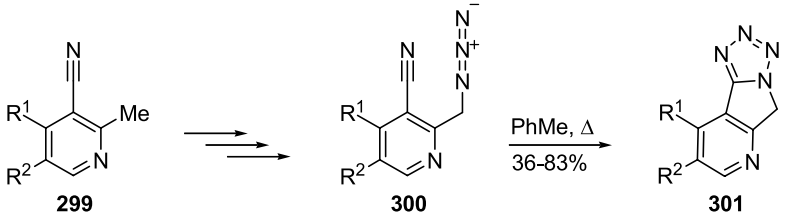
Simple heating of the starting material in solution at 130–140 °C usually provides a pure product [208].



Scheme 60 Common route to tetrazoles **298** via imidoyl azides **297** which spontaneously cyclize [208]

Some applications of intramolecular tetrazole formations are known, and two examples are described below.

Lukyanov et al. synthesized 2-azidomethyl-3-cyanopyridines **300** starting from nicotino-nitriles **299** (Scheme 56) [193], which, via **300**, undergo an intramolecular cycloaddition to give 5*H*-tetrazolo[1′,5′:1,5]pyrrolo[3,4-*b*]pyridines **301** (Scheme 61) [209].



Scheme 61 Reaction pathway to tricyclic tetrazolylpyridines **301**, starting from nicotino-nitriles **299** [209]

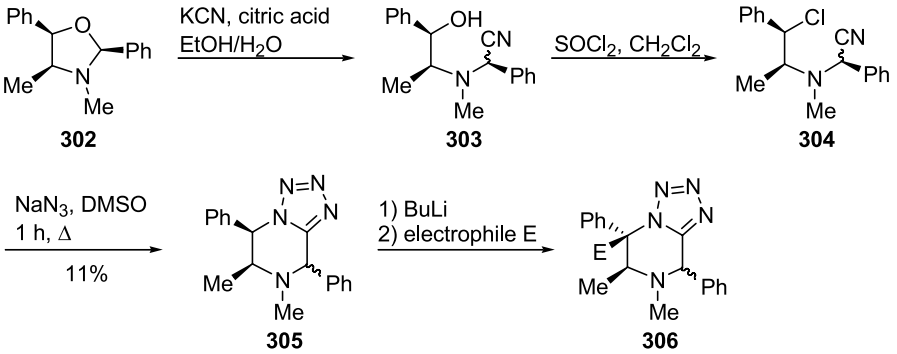
The cycloaddition reaction proceeds by heating the 2-azidomethyl-3-cyanopyridines **300** in toluene to 130–140 °C for 90 h. Those structures could serve as a template for combinatorial libraries.

Another application was shown with β-amino alcohols being converted into fused tri- and tetrazolo-piperazines by Couty et al. [210] with high diastereoselectivity and regioselectivity depending on the substitution pattern of the starting material (Scheme 62).

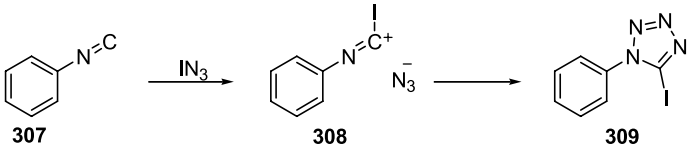
The alcohol **303** is converted into a chloride **304** which can be replaced afterward by an azide group. Intramolecular cyclization gives tetrazolo-piperazines **305**. The cycloaddition is carried out in DMSO under heating (110–150 °C).

Beside all described syntheses of tetrazoles from nitriles and azides, 1-substituted tetrazoles, which are synthesized from isonitriles, have also received much attention [177–179].

One example of an uncatalyzed, intramolecular cycloaddition between isonitriles and azides was described in 1967 by Levy et al. [211]. They introduced the azide function into molecules by using iodine azide (Scheme 63).



Scheme 62 Synthesis of fused tetrazolo-piperazines **306** using readily available starting materials. Those structures can be further functionalized diastereoselectively by using anionic chemistry [210]



Scheme 63 Reaction of isonitriles **307** with iodine azide towards 1,5-substituted tetrazoles **309** [211]

Following this reaction route allows the synthesis of 5-iodotetrazole **309**. The reaction involves a nitrilium ion **308** which adds azide ion to produce the tetrazole **309**.

5.2 Catalyzed Reactions

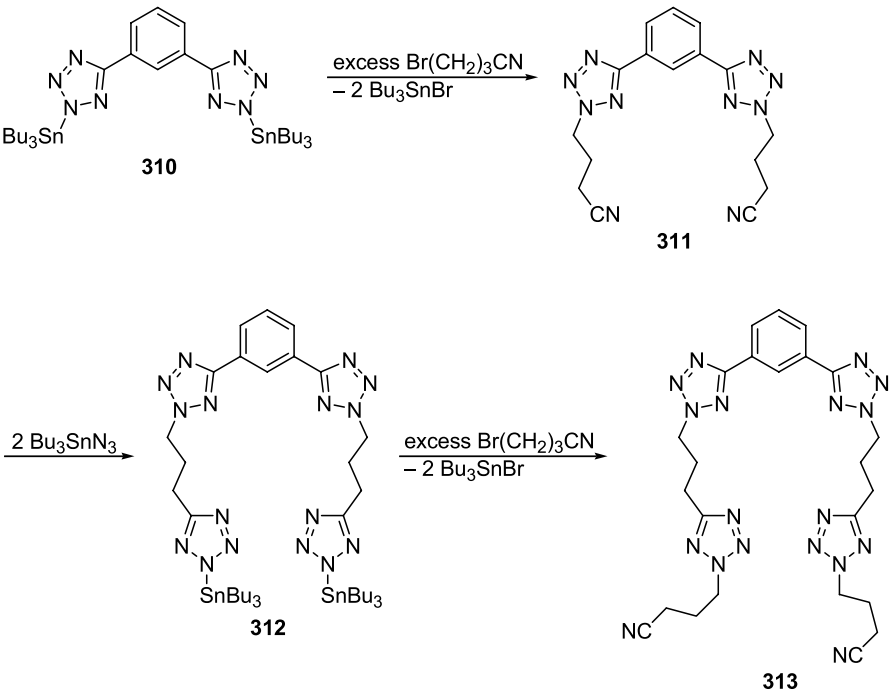
While the most direct method to form tetrazoles proceeds via concerted (uncatalyzed) [2+3] cycloaddition between organic azides and organic nitriles, this cycloaddition is too slow for synthetic purposes (except in the case of activated nitriles). This disadvantage can be avoided if azide salts are used and if the cycloaddition is catalyzed. This variant might be of greater synthetic interest since the range of nitriles is broader and a wide variety of metal-azide complexes can serve as azide donors [188, 212–219].

5.2.1 Intermolecular Cycloaddition Reactions of Azides

Molloy et al. have been investigating the use of organotin azides, as such species readily react with nitriles in cycloaddition reactions to give tetrazoles as precursors to functionalized poly-tetrazoles. Those substances can

be used as acidic ligands towards other metals which themselves form unstable azides and are hence not suitable to direct synthesis via cycloaddition reactions [220].

In this scheme, an excess of 1-bromo-3-cyanopropane reacts with 1,3-bis[2-(tributylstannyl)tetrazole-5-yl]benzene (**310**) [221] to yield **311**, which can subsequently be converted to **312** by a cycloaddition reaction with Bu_3SnN_3. **312** reacts further with $Br(CH_2)_3CN$ to give **313** (Scheme 64).



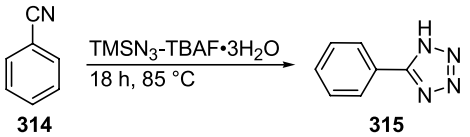
Scheme 64 Synthesis of multi-functional tetrazoles by sequential introduction of pendant nitriles [220]

The cycloaddition between Bu_3SnN_3 and RCN affords an efficient route to novel tetrazoles, which can be isolated in their non-metallated (N–H) form by reaction with HCl.

Besides tin, zinc derivatives were investigated in cycloaddition reactions. It has been shown that zinc salts are excellent catalysts for the cycloaddition reaction [222, 223], even in aqueous media, thereby enabling a more environmentally friendly route to 1*H*-tetrazoles [224, 225]. Himo et al. have performed model calculations using density functional methods to investigate the role of zinc. The calculations focused on acetonitrile, whereas the conclusions should be of direct relevance to nitriles in general. First calculations indicated that the coordination of an azide anion to ionic Zn does not

lead to any significant change in the energy barriers. The situation was considered where the zinc ion is bound to the nitrile and methyl azide comes from outside the coordination sphere. Here, the models showed some lowering in the energy barrier, so that coordination of the nitrile to the Zn ion is the main catalytically active species [212].

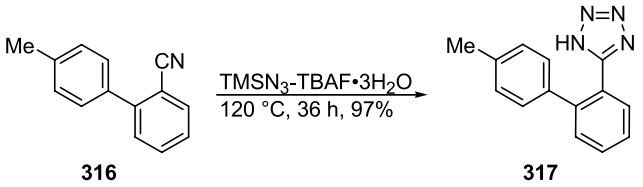
Most of the described procedures of forming tetrazoles (catalyzed and uncatalyzed) suffer from some disadvantages like the use of both toxic metals and expensive reagents, drastic reaction conditions, water sensitivity, and the presence of dangerous hydrazoic acids. The zinc(II)-catalyzed reactions to form tetrazoles by Sharpless and coworkers [212, 224, 225] are safe, but in the case of sterically hindered aromatic or alkyl inactivated nitriles, high temperatures (140–170 °C) are required. Amantini et al. reported TBAF to be an efficient catalyst in the synthesis of 5-substituted 1*H*-tetrazoles by using $TMSN_3$ without solvents (Scheme 65) [226].



Scheme 65 TBAF-catalyzed synthesis of 5-substituted 1*H*-tetrazoles without solvents [226]

No silylated compounds were detected under these reaction conditions, showing that the use of TBAF was two-fold advantageous, for the activation of the azide nucleophile on one hand and the deprotection of *N*-silylated products on the other hand.

Furthermore, this procedure can be applied to aryl and alkyl organic nitriles, leading in each case to the formation of tetrazoles in excellent yields. For example, the reaction of a sterically demanding biphenyl nitrile **316** was successful. The resulting tetrazole **317** is a subunit that has become ubiquitous in some of the most potent angiotensin II antagonists (Scheme 66) [226].



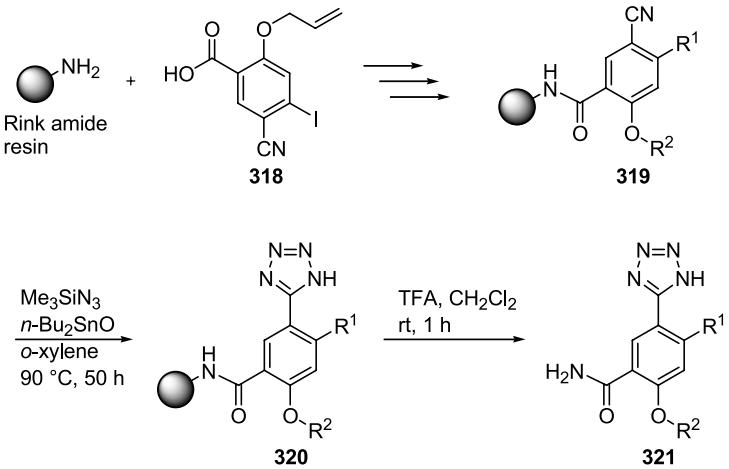
Scheme 66 Reaction of a sterically demanding biphenyl nitrile **316** to the corresponding tetrazole **317** [226]

Another way to catalyze the [2+3]-cycloaddition was published by Kantam et al. They used nanocrystalline ZnO as a heterogeneous catalyst [227]. The reactions were carried out using sodium azide in DMF at 120–130 °C.

Nanocrystalline ZnO was recovered quantitatively by centrifugation and could be reused at least for three cycles with minimal loss of activity. Interestingly, phthalonitrile afforded the monoaddition product, whereas in the presence of Zn(II) salts, the diaddition product [172, 208, 212, 224, 225] was reported [227].

Bräse et al. showed tetrazole formation via cycloaddition on solid supports, following a strategy of Wittenberger [217, 228]. For the solid phase synthesis, 2-allyloxy-5-cyano-4-iodo benzoic acid (**318**) was synthesized as a key intermediate. This substrate was then attached to a Rink amide Merrifield resin and was further functionalized.

Prior to cleavage from the solid support, the nitrile **319** was reacted with Me_3SiN_3 (**146**) in order to give the tetrazoles (Scheme 67) [228].

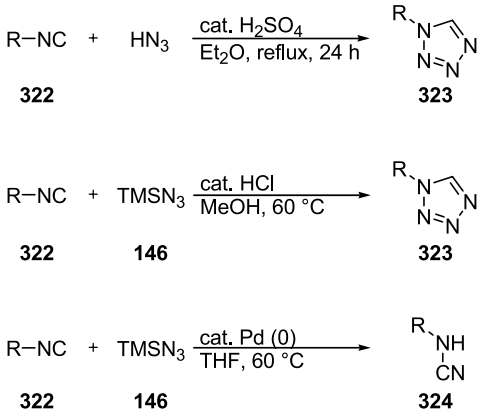


Scheme 67 Tetrazole ring formation from a resin-bound nitrile **319** with Me_3SiN_3 (**146**) and catalytic *n*-Bu_2SnO for 50 h at 90 °C in *o*-xylene [217, 228]

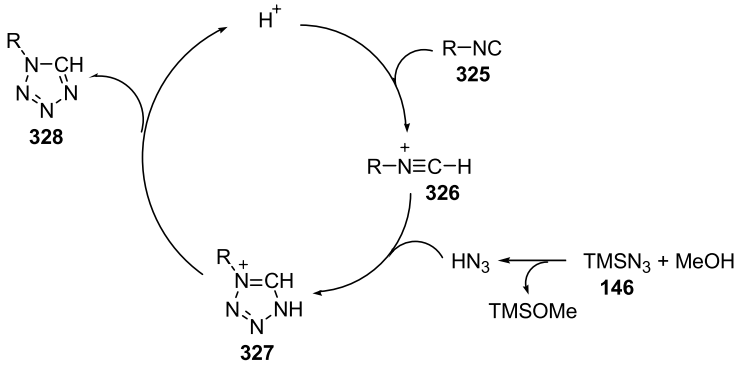
Additionally, for catalyzed reactions, an example for synthesis of tetrazoles by reacting isonitriles and azides was reported. Yamamoto et al. reported that the acid-catalyzed [3+2] cycloaddition between isocyanides **322** and trimethylsilyl azide (**146**) in the presence of methanol gives the desired 1-substituted tetrazoles **323** in good yields (Scheme 68) [177–179].

It was observed that HCl gave the highest yields, although catalysts such as $CeCl_3$ and $ZnCl_2$ were also effective. A proposed mechanism for the 1-substituted tetrazoles-forming reaction was also presented (Scheme 69).

At the initial stage of the cycle, an isocyanide **325** reacts with H^+ to yield intermediate **326**, which could undergo a cycloaddition with the in situ formed HN_3 to give **327**. Deprotonation of the intermediate **327** finally affords the 1-substituted tetrazoles **328** (Scheme 69).



Scheme 68 Acid-catalyzed cycloaddition between isonitriles **322** and azides [177–179]



Scheme 69 Proposed mechanism for the formation of tetrazoles **328** [177–179]

Because intramolecular cycloaddition reactions with azides work well by simple heating, no catalyst is required, and as a consequence, no such catalyzed reactions are described.

6
Selected Applications of Azide Cycloaddition

6.1
Bioconjugation Reactions

Since the development of the click chemistry concept by Sharpless and coworkers [59], the well known Huisgen 1,3-dipolar cycloaddition of azides and alkynes to 1,4-disubstituted 1,2,3-triazoles [229] has regained much atten-

tion. In particular, the discovery by Sharpless and co-workers [50] as well as by Meldal and co-workers [51] that copper(I) is a suitable catalyst in this conversion led to a true revival of the Huisgen 1,3-dipolar cycloaddition reaction [230]. The advantages of this type of reaction are its simple experimental procedure, the high degree of regioselectivity and the almost quantitative transformation under extremely mild conditions. Alkyne and azide groups as organic functionalities are very small in size and are highly energetic with particularly narrow distribution of reactivity. They can be conveniently introduced into organic compounds and are quite indifferent towards many solvents, pH and a wide variety of other functional groups or biological systems. Consequently, these properties allow the covalent linkage of biomolecules, also known as bioconjugation, even in an aqueous environment under mild physiological conditions with high efficiency and chemoselectivity. Hence, the Cu(I)-catalyzed click reaction between azide and alkyne groups giving 1,2,3-triazoles is of particular interest for chemists as well as for molecular biologists in terms of biomolecular and biomedical research [74, 231].

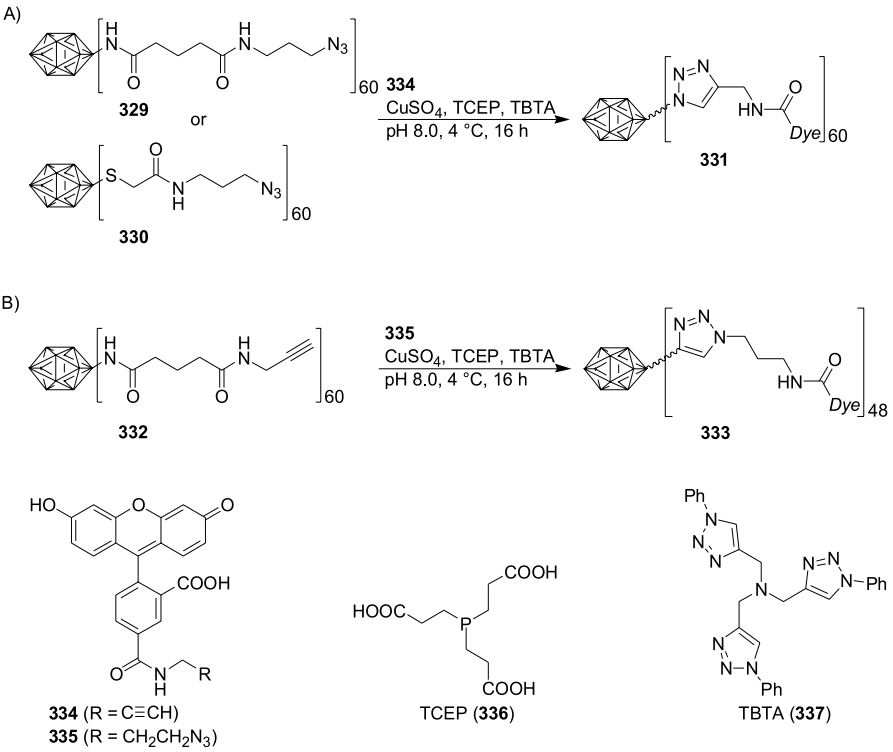
Recently, reports on different applications dealing with Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions between azides and alkynes in the field of bioconjugation were published. These applications comprise tagging and modifying of live organisms or proteins such as virus particles [59, 60], cells [63–66] or enzymes [232], to study their involvement in biological processes or to detect their biodistribution and metabolism. The activity-based protein profiling (ABPP) in complex tissue lysates [233] as well as labeling of DNA [234] are further innovative developments in this field, to mention a few.

6.1.1 Tagging of Live Organisms and Proteins

The application of mild methods for the chemical modification of components in or on living organisms under physiological conditions has gained much interest in the past few years [235–237]. With the discovery of the mild Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of azides and alkynes, another powerful tool was provided for chemically modifying live organisms and proteins [74, 231].

The icosahedral cowpea mosaic virus (CPMV) in its intact form is a robust platform for organic reactions on a live system. It is composed of 60 identical copies of an asymmetric two-protein unit assembled around a single-stranded RNA. Each unit consists of one reactive lysine residue and genetic engineering allows the additional insertion of one reactive cysteine residue per unit which enables the attachment of suitable molecules by chemical reaction. CPMV can be made inexpensively on the gram scale and it is very easy to separate the chemically modified viral particles from unreacted small reagents [238, 239]. Therefore, CPMV is an ideal model system to test bioconjugation reactions on a live organism.

Finn and co-workers used the CPMV system to attach a total of 60 azides per virus particle to either the NH_2 or the SH function by using conventional bioconjugation techniques and received azide-modified CPMV **329** and **330** (Scheme 70A). According to this, 60 alkynes were attached per virus particle in another experiment, too, and alkyne-modified CPMV **332** was obtained (Scheme 70B). Consequently, the virus particles displayed the azide or alkyne groups at the surface of the capsid and were then subject to Cu(I)-catalyzed 1,3-dipolar cycloaddition with alkyne- or azide-modified fluoresceine **334** or **335** to yield live fluoresceine-tagged CPMV viruses **331** or **333**. To protect the virus from Cu-triazole-induced disassembly, the reaction conditions were optimized. The 1,3-dipolar cycloaddition was found to proceed best with a mixture of copper(II)-sulfate, tris(2-carboxyethyl)phosphine (TCEP, **336**) and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA, **337**). TCEP (**336**) acts as an in situ reducing agent for $CuSO_4$ while TBTA (**337**) enhances the reaction rate greatly, stabilizes the resulting Cu(I) and inhibits oxidative alkyne coupling. Using these conditions, each of the 60 azide groups on the virus

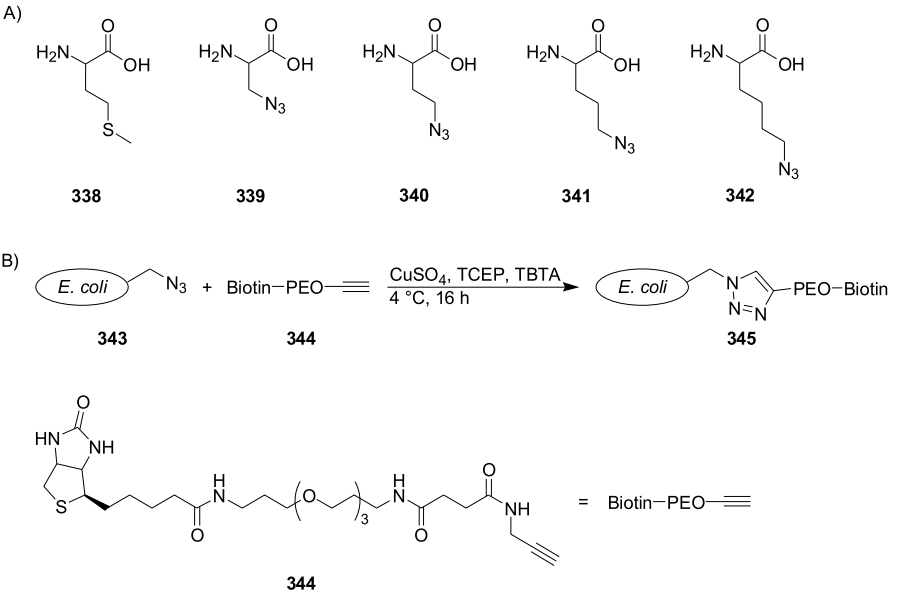


Scheme 70 **A** Labeling of azide-modified cowpea mosaic virus particles **329** and **330** with alkyne-derivatized fluoresceine **334**, **B** labeling of alkyne-modified cowpea mosaic virus particles **332** with azide-derivatized fluoresceine **335** [60]

surface of **329** and **330** reacted in the 1,3-dipolar cycloaddition with alkyne-modified fluoresceine **334** with a yield of 96% (Scheme 70A). In contrast, only 48 of the 60 alkyne groups of the alkyne-modified virus particles **332** reacted with azide-modified fluoresceine **335** in this environment with a yield of 80% (Scheme 70B) [60]. Beside azide- or alkyne-modified fluoresceine, further azide- or alkyne-modified dyes, which in part display superior solubility in water and have good optical properties, were applied to tag CPMV by click bioconjugation [240, 241].

The presentation of proteins and polypeptides on the cell surface is a technology that is useful for applications ranging from the screening of antibody fragments to the creation of whole cell bioremediation agents [242]. Though these approaches are rather innovative, they are limited by the fact that the proteins and peptides displayed on the cell surface are composed of just the canonical amino acids. Therefore, some efforts have been made to extend the chemical functionalities available on the cell surface [235, 243, 244].

Tirrell and co-workers used molecular biology techniques to replace methionine residues in the outer membrane protein C (OmpC) of *Escherichia coli* cells by the non-natural amino acid azidohomoalanine **340** (Scheme 71A). These bacterial cells **343**, now presenting azide groups on the outer membrane surface, were subsequently tagged with a biotinylated alkyne reagent **344** by using TCEP (**336**), TBTA (**337**) and $CuSO_4$, leading to **345** in a 1,3-di-



Scheme 71 **A** Structures of methionine **338**, azidoalanine **339**, azidohomoalanine **340**, azidonorvaline **341** and azidonorleucine **342**. **B** Tagging of azide-modified *E. coli* cells **343** with a biotinylated alkyne reagent **344** [65, 245]

polar cycloaddition (Scheme 71B). Using this technique, the incorporation of the non-natural amino acid **340** into OmpC is detectable by staining with fluorescent streptavidin, facilitating flow cytometric separation of labeled and unlabeled cells [65]. Further studies revealed that highly pure CuBr allowed cell surface labeling to be enhanced by a factor of 20. This led to the discovery that even azidoalanine **339** (Scheme 71A), which was previously not thought to be a good replacement for methionine **338** in protein synthesis, was incorporated into cell surface proteins. Furthermore, the incorporation of the larger amino acids azidonorvaline **341** and azidonorleucine **342** (Scheme 71A) into *E. coli* as a substitute of methionine **338** was demonstrated [245].

In addition, a simplified approach to protein labeling was described by using histidine-tagged barstar (model protein), to which homopropargylglycine (Hpg, **346**) and ethynylphenylalanine (Eth, **347**), both containing alkyne groups, were incorporated by expression (Fig. 2).

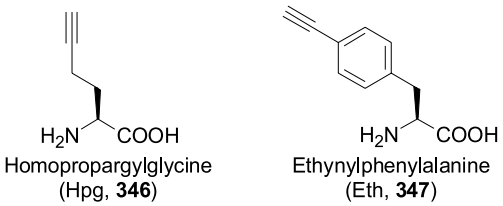


Fig. 2 Structures of the non-natural amino acids homopropargylglycine **346** and ethynylphenylalanine **347** [246, 247]

These amino acids **346** and **347** serve as analogues of methionine (Met, **338**) and phenylalanine (Phe). Once the protein containing Hpg (**346**) and Eth (**347**) is expressed, *E. coli* cell cultures **348** are allowed to react with an azide derivative of coumarin **349** in the presence of Cu(I) catalyst and TBTA (**337**) to **350** (Fig. 3) [246, 247].

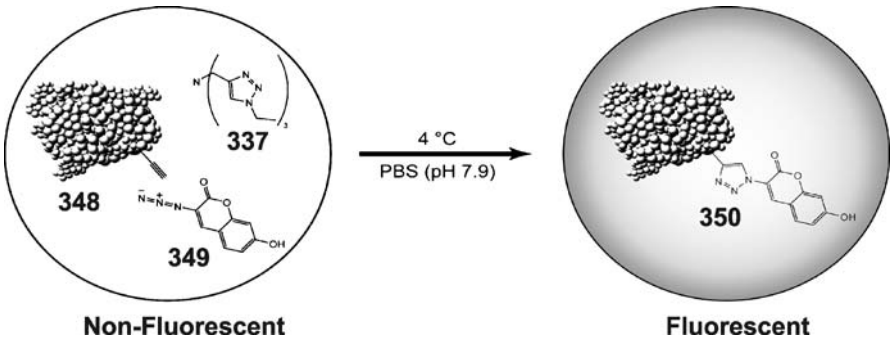
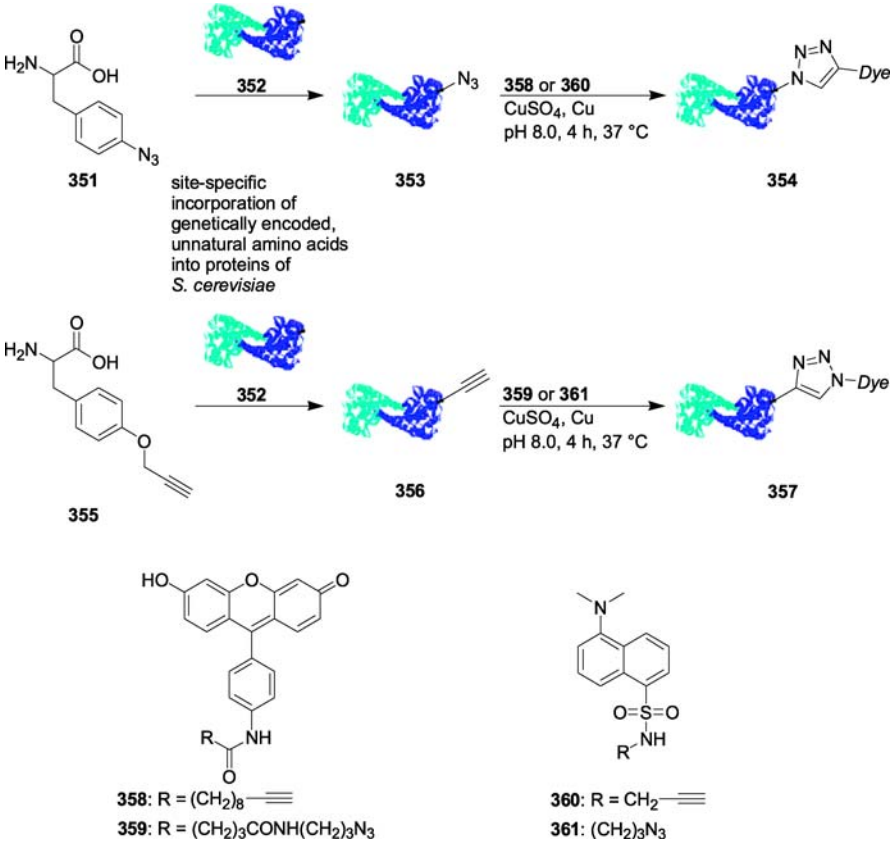


Fig. 3 Protein labeling in *E. coli* cell cultures with azide derivatives of coumarin **349** [246, 247]

Confocal microscopy was employed to examine fluorescence and only the cells containing barstar proteins with non-natural amino acids were fluorescent. Thus, alkyne-azide coupling can be used as an effective method of protein labeling in bacterial cells.

A site-specific, fast, reliable and irreversible method of bioconjugation to an enzyme was reported by Schultz and co-workers. They first incorporated genetically encoded unnatural amino acids, like *p*-azidophenylalanine (**351**) or *O*-propargyltyrosine (**355**), into proteins **352** of the yeast *Saccharomyces cerevisiae*. Then the azide- or alkyne-containing yeast **353** or **356** was subjected to a 1,3-dipolar cycloaddition with azide- or alkyne-containing dyes **358** to **361** to give the corresponding triazole **354** or **357**. Afterwards, gel-fluorescence scanning of the modified protein was possible (Scheme 69) [232]. This methodology for genetically encoding unnatural amino acids in prokaryotic and eukaryotic organisms was used in conjunc-



Scheme 72 Site-specific tagging of *Saccharomyces cerevisiae* proteins **352** using click chemistry [232]

tion with phage display to synthesize polypeptide libraries with unnatural amino acid building blocks [248]. For this study, a pIII fusion streptavidin-binding peptide was expressed in *E. coli* strain TTS (type III secretion) in the presence of unnatural amino acids. The resulting phages displayed the peptides which bear the unnatural amino acids. In order to characterize this phage display system, the resulting phages were tagged with an alkyne dye via 1,3-dipolar cycloaddition using the Tirrell conditions [65]. SDS-PAGE and Western blot analysis showed that the unnatural amino acid was specifically introduced into the pIII coat protein of the unnatural phage. This technology enables the site-specific and irreversible attachment of a single PEG molecule to a protein, making the production of well defined and homogenous therapeutic PEGylated proteins possible [249].

6.1.2 Activity-Based Protein Profiling (ABPP)

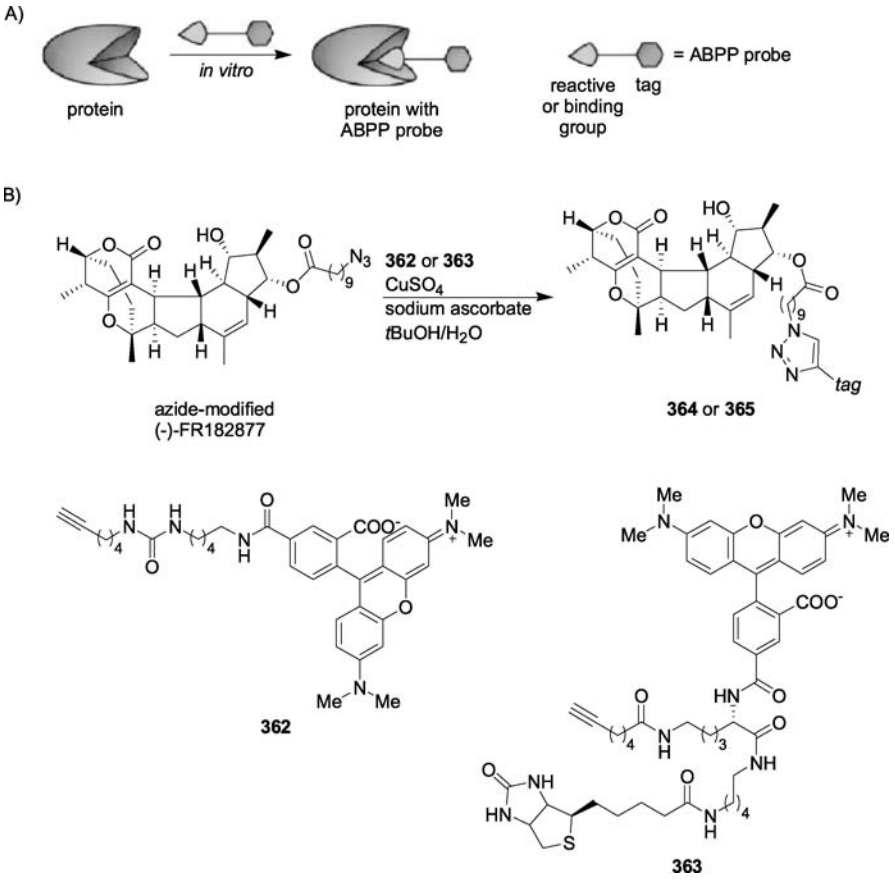
Recently, genome sequences of numerous prokaryotic and eukaryotic organisms have become available and set the cornerstone for understanding the molecular basis of life in its many forms. However, the information content of genome sequences is quite limited and is not able to explain the complex physiological and pathological processes which are in general controlled by protein and RNA molecules, the products of gene expression. To convert this flood of molecular information provided by genome sequencing into a deeper appreciation of cell biology, new strategies for the systematic analysis of gene products have become necessary [250].

The relatively new field termed proteomics deals with the assignment of molecular and cellular functions to the tens of thousands of protein products encoded by prokaryotic and eukaryotic genomes. In addition, it seeks to develop and apply new methods for the global analysis of protein expression and protein function. These methods must fulfill distinct requirements ranging from the analysis of many proteins in parallel and in samples of high complexity up to the characterization of proteins in a dynamic cellular environment, in which these biomolecules are subject to a myriad of post-translational modifications and actions of various activators and inhibitors [250, 251].

Activity-based protein profiling (ABPP) is a rather new post-genomic method pioneered by the Cravatt group that differs fundamentally from the conventional abundance-based methods of proteomics [252–254]. ABPP uses active site-directed probes to tag proteins and to monitor their expression levels and function in complex proteomes. For example, it distinguishes an active enzyme from its inactive precursors and inhibitor-bound forms. The ABPP probes are composed of two main elements. First, they contain a reactive group which selectively binds to and covalently labels the active site of the corresponding protein, or a binding group that promotes probe interactions with particular active sites of the corresponding protein, respectively.

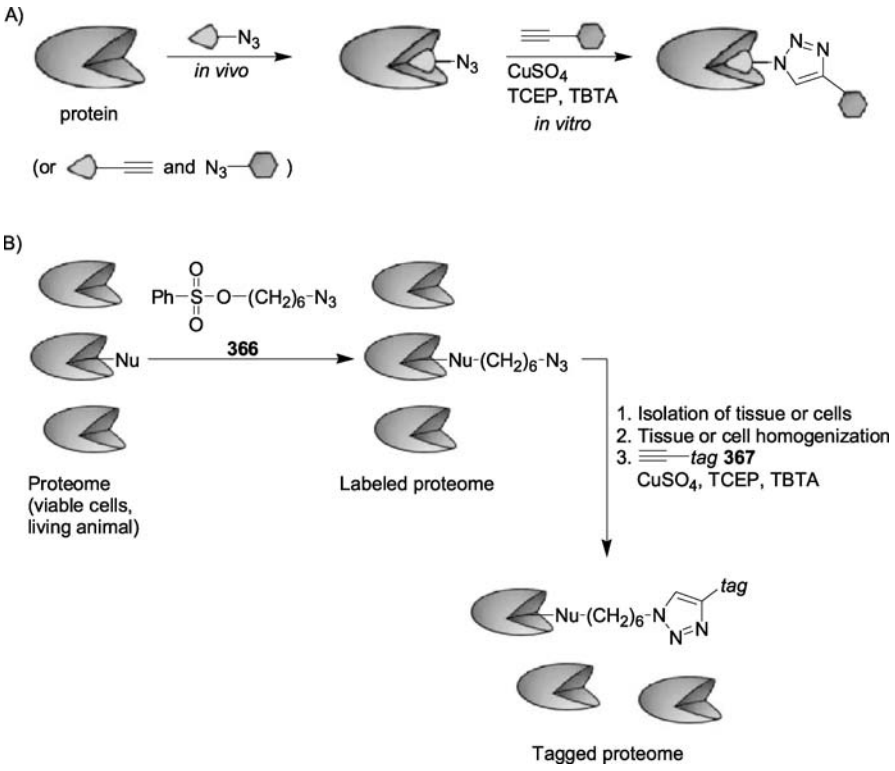
Secondly, they comprise one or more reporter tags which enable the rapid detection and isolation of the labeled protein (Scheme 73A) [252, 255].

FR182877, a natural product from a *Streptomyces* fermentation broth with several interesting biological properties [256, 257], was investigated by Cravatt and co-workers using the ABPP technique in order to discover its mechanism of action. They synthesized Rhodamine- and Rhodamine-biotin-tagged FR182877 analogues **364** and **365** using the Cu(I)-catalyzed triazole process. The tagged FR182877 derivatives **364** and **365** were subsequently incubated with mouse proteome in vitro and led to the identification of carboxylesterase-1 (CE-1) as a specific target protein of this natural product. Further examinations demonstrated that FR182877 is a potent and selective inhibitor of CE-1 with an IC_{50} value of 34 nM (Scheme 73B) [258].



Scheme 73 **A** Principle of conventional activity-based protein profiling (ABPP) [255]. **B** Synthesis of Rhodamine- and Rhodamine-biotin-tagged molecules **364** and **365** of the natural product FR182877 in order to investigate its mechanism of action by the conventional ABPP technique [258]

To date, ABPP probes have been developed for several enzyme classes and were successfully applied, but the commonly used reporter groups, like fluorophores or biotin, are quite bulky. This in turn implies that the reporter tags are often cell wall impermeable and require cell or tissue homogenization prior to analysis, making measurements in living cells and organisms impossible [252]. To circumvent this drawback, Cravatt and coworkers developed an innovative advancement of the conventional ABPP in which the reporter group is attached to the activity-based probe after covalent labeling of the protein targets. Azides and alkynes were employed as bioorthogonal coupling partners to link probe and tag by using the Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction (Scheme 74A). By means of this method, Cravatt and co-workers detected glutathione *S*-transferase (GSTO 1-1), aldehyde dehydrogenase (ALDH-1) and enoyl CoA hydratase (ECH-1) at endogenously expressed levels in viable cells. For these studies, an azide-derivatized and tag-free, cell-permeable phenylsulfonate ester probe



Scheme 74 **A** Principle of using click chemistry for tag-free activity-based protein profiling [255]. **B** Activity-based protein profiling in viable cells or in living animals using click chemistry with cell-permeable phenylsulfonate ester probe (PS-N_3, **366**) and an alkyne-modified tag **367** [233]

(PS-N_3, **366**) was incubated with intact cells and only enzymes which exhibited a nucleophilic site, then reacted with PS-N_3 (**366**) in order to give an activity-based probe. After cell homogenization, a Rhodamine alkyne (Rh-alkyne) tag **367** was attached to the azide bearing probe by Cu(I)-catalyzed triazole formation (Scheme 74B). Protein separation from excess reagents by centrifugation and subsequent analyzes by SDS-PAGE and in-gel fluorescence scanning led to results that were consistent with conventional methods [233].

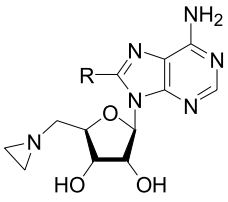
This click chemistry-based approach to ABPP even works in live animals to determine specific protein expression levels. As an example, PS-N_3 (**366**) was injected into living mice to investigate ECH-1 expression in the heart tissue. One hour after injection, the mice were sacrificed, and ECH-1 was successfully detected by staining the crude heart-homogenate via Cu(I)-catalyzed bioconjugation using a Rh-alkyne tag **367** (Scheme 74B) [233].

The drawback of this newly developed ABPP methodology is a higher degree of background labeling as compared to conventional ABPP, due to low-level non-specific labeling of abundant proteins of the proteome. Further in detail studies demonstrated that swapping the reaction groups, for example PS-alkyne/Rh-N_3 instead of PS-N_3/Rh-alkyne, reduced the extent of background labeling and enabled the visualization of lower-abundance enzyme activity. However, the PS-N_3/Rh-alkyne combination was shown to react four times faster, making it the system of choice for rapid analysis [255].

6.1.3 Labeling of DNA

Another application of "click chemistry" in biological systems was described by Rajski et al. They investigated the sequence-selective targeting of DNA, a method for covalent site-specific DNA alkylation mediated by methyltransferases (MTases) that enables subsequent chemoselective ligation via the Huisgen [2+3] cycloaddition reaction. During biological methylation, the transferred methyl group is derived from *S*-adenosyl-L-methionine (SAM) [259], which under the direction of MTases is a highly selective alkylation agent for DNA, RNA and protein modification and is an important biosynthetic tool for secondary metabolite production [260]. The investigation of the mechanisms of biological methylation, particularly in gene transcription, was hampered by a lack of tools for the identification of MTase substrates, with the largest impediment arguably originating from the methyl group's relative absence of functionality.

Aziridine adenylates **368** (Scheme 75) take part in MTase dependent DNA alkylations [261–263], where the aziridines are believed to undergo quarternization of the 5′-amine followed by MTase binding, delivery to the site of methylation, and subsequent aziridinium ring opening with concomitant substrate alkylation.

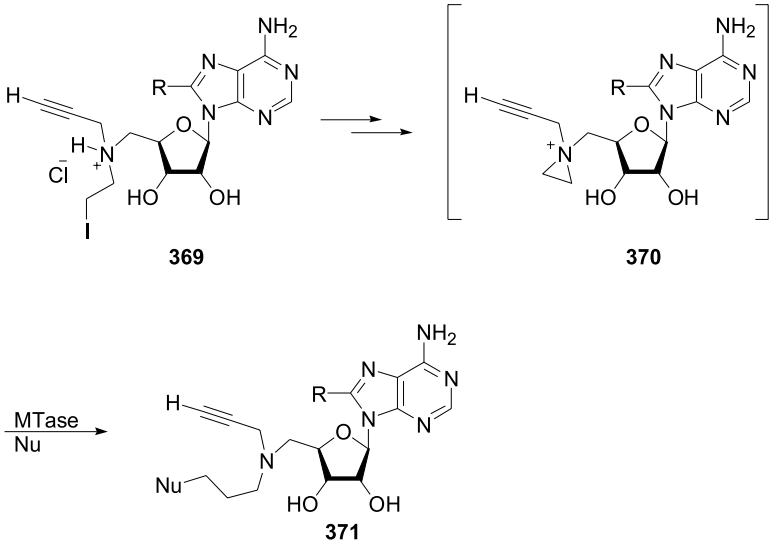


368

R = H, N_3, $NH(CH_2)_4N_3$

Scheme 75 Structure of 5′-aziridine adenylates **368** as MTase-dependent DNA-modifying agents [264]

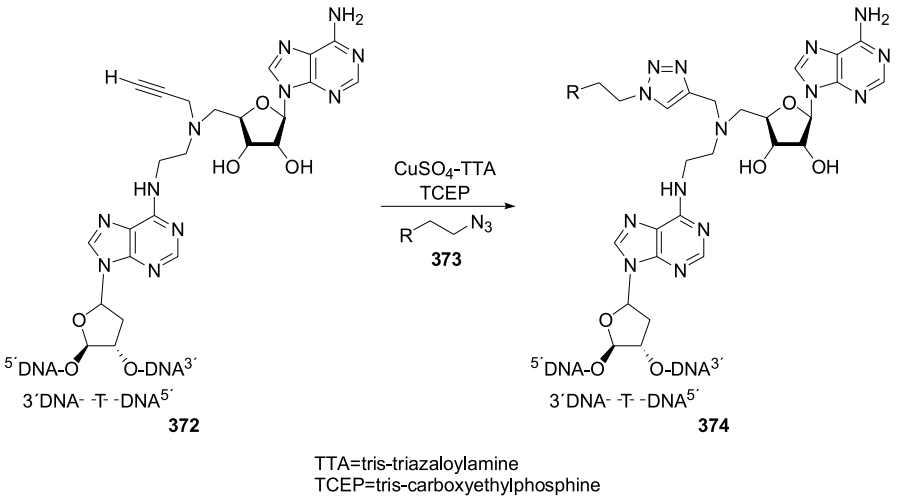
Rajski et al. exploited the described mechanisms in the design of a novel synthetic cofactor. Hydrochloride salt **369** was envisioned to rapidly form aziridinium species **370** in situ, whereas this intermediate was expected to be more reactive and more amenable towards MTase-promoted chemistry (Scheme 76).



Scheme 76 Proposed aziridinium ion formation [264]

By virtue of the propargyl substituent of **369**, efficient and predictable site-specific alkylation of nucleic acids with the possibility of bioconjugation via Huisgen [2+3] cycloaddition can occur. Thus, DNA lesion of **372** could afford triazole **374** following reaction with alkyl azides **373** (Scheme 77).

In this system, two important concepts came to light. First, synthetic co-factors need not be restricted to 5′-aziridines, which have proved to be rather



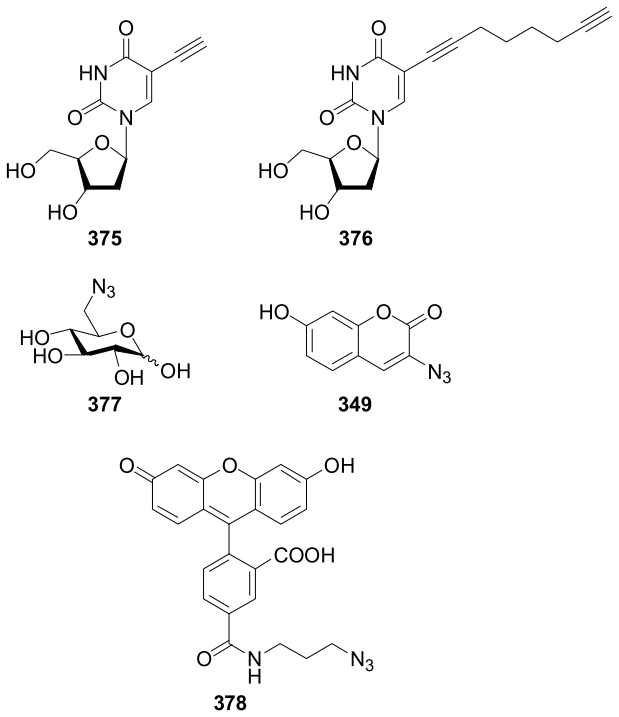
Scheme 77 Proposed Huisgen cycloaddition with alkyne-modified DNA **372**. TTA was used as ligand for copper(I) and TCEP as reductants for $CuSO_4$ [264]

elusive synthetic targets. Thus, MTase-dependent delivery of **369** to DNA is not restricted to small duplexes. Secondly, DNA can take part in click chemistry, and **369** represents a novel means by which to perform such chemistry in a sequence-selective manner [264].

In 2006, Carell et al. took the described concept further and reported that click chemistry can be used as a method for high-density post-synthetic functionalization of alkyne-modified DNA. Thereby, small chemical reporter groups are incorporated into particular genes that can be further functionalized (termed post-synthetic functionalization) [265].

The construction of modified oligodeoxyribonucleotides (ODNs) bearing alkyne reporter groups (Scheme 78) in high density was reported, as well as the development of a click reaction protocol which enables loading of DNA in high yields with a variety of molecular labels [266]. This two-step process involving the enzymatic incorporation of an alkyne-nucleoside building block and post-synthetic functionalization can be used to decorate DNA for identification or isolation according to the nature of the probe.

The click reaction with ODNs containing alkyne **375** did not produce quantitative conversion of the fluorescent click product, whereas a flexible ODN alkyne series with the alkyne spacer nucleoside **376** showed fully labeled products. Therefore, it is possible to achieve highly reliable and complete functionalization of ODNs. To investigate whether the method can be used to label long DNA fragments, two PCR primers (ODN-**379** and ODN-**380**) containing two click sites were synthesized and subsequently used in PCR. The purified DNA was then treated with azide **378** using the CuBr/ligand method [65, 245–247]. Gel electrophoresis of the reaction product showed



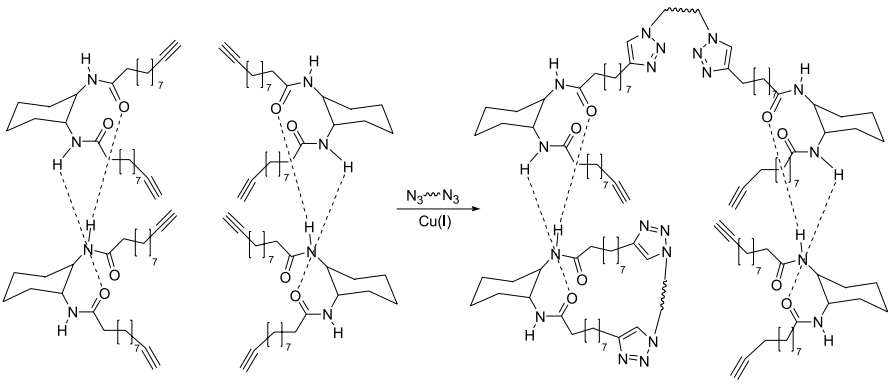
Scheme 78 Modified oligodeoxyribonucleotides **375** and **376**, bearing alkyne reporter groups and azides **349**, **377** and **378** as markers via click reaction [266]

only a single band corresponding to a fluoresceine-labeled click product. Therefore, the method can even be employed in order to modify long DNA fragments obtained by PCR without DNA cleavage.

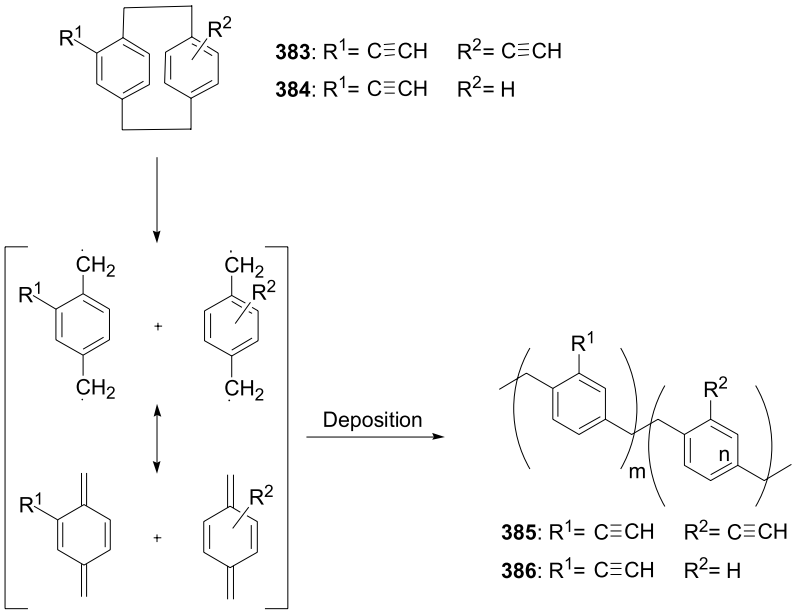
6.2 Material Sciences

Although click chemistry was initially postulated as a general concept for organic synthesis, this strategy also has an enormous potential in material science [70, 267]. The first report that illustrated this point appeared in mid-2004 by Hawker, Fokin, Sharpless and co-workers [67]. Afterwards, the popularity of click chemistry within the material science community grew considerably and has been, in particular, significantly boosted by the innovative works of Hawker, Fréchet and Finn [67, 95, 268–270], see also [271]. Dendrimers are large regularly branched synthetic molecules which continue to receive much attention due to their unique properties and applications in medicinal chemistry. Problems like difficulties of purification and lengthy chromatographic separations of impure products have been addressed by the

fidelity of CuAAC. Fokin et al. demonstrated the first dendrimer synthesis applying click chemistry. Utilizing Fréchet's convergent approach, individual branches or dendrons were built sequentially by click reactions and then coupled to a multivalent center piece in the last step [67]. The experimentally simple reaction proceeded well in aqueous solution without protection from oxygen requiring only stoichiometric amounts of starting material.



Scheme 79 Cross linking of organogelators using azide cross-linkers [272]



Scheme 80 Synthesis of alkyne-containing polymers **385** and **386** by chemical vapor deposition of diethynyl[2,2]paracyclophane (**383**) and 4-ethynyl[2,2]paracyclophane (**384**) [273]

Organogels, useful substances for biomedical applications ranging from drug delivery to tissue engineering scaffolds, are substances which undergo molecular self assembly. Their aggregation into fibrous networks is driven by multiple weak interactions such as dipole–dipole, Van der Waals and hydrogen bonding. One example of cross linking hydrogens employing CuAAC is shown in Scheme 79 [272]. Finn et al. used low molecular weight organogelators, based on the undecynylamide of *trans*-1,2,diaminocyclohexane.

Further advances in the design of biologically active interfaces require novel strategies for the robust and specific attachment of biological ligands onto surfaces. Lahann et al. recently reported on a new type of biological surface, based on alkyne-containing vapor-deposited polymer coatings [273]. These reactive coatings are applicable to a wide range of substrates and can be modified by subsequent spatially directed click chemistry. The alkyne-containing polymer **386** has been found to show remarkable reactivity towards azides through the chemoselective Huisgen 1,3-dipolar cycloaddition reaction. In contrast to the dialkyne containing polymer **385**, reactive coating **386** showed excellent adhesion and stability at elevated temperature and in solvents.

7 Conclusion and Outlook

The cycloaddition of azides with double and triple bonds to yield heterocyclic structures – albeit being discovered many centuries ago – has been evolved into a powerful tool in organic synthesis, material sciences and life sciences.

In particular, the recent development of catalytic and therefore mild reaction conditions has led to an enormous increase of systematic investigation and novel applications. One can expect that this growth will continue further and will have a sustainable impact on organic synthesis.

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Enantioselective Cycloadditions of Azomethine Ylides

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Abstract The asymmetric 1,3-DCR of azomethine ylides, which is generated from the corresponding imino ester and alkenes, is one of the most fascinating transformations because the configuration of the four new stereogenic centers of the finally obtained proline can be absolutely established in only one step with total atom economy. Since 2002, the catalyzed enantioselective 1,3-DCRs have been performed using chiral metal complexes. For example, chiral silver and copper complexes are the most employed catalysts. Silver complexes afforded selectively *endo*-cycloadducts, however, both *exo*- and *endo*-adducts were generated in the presence of several chiral Cu(I) complexes. Although chiral zinc complexes have also been studied in *endo*-selective processes, the published works are not so numerous. Bidentate ligands, such as bisphosphanes, nitrogenated phosphanes, and sulfur-containing phosphanes have shown very high enantioselectivity levels. Apart from the employment of chiral Lewis acids, the utilization of chiral bases or organocatalysts are also known, albeit with a large number of limitations and, in some cases, with lower enantioselections.

Keywords Asymmetric catalysis · Azomethine ylides · Chiral ligands · Cycloaddition · Prolines

Abbreviations

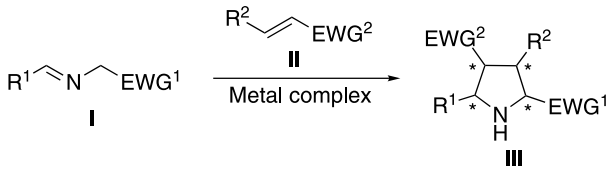
Ac	Acetyl group
Ar	Aryl group
Bicp	(*R*,*R*) or (*S*,*S*)-2,2′-bis(diphenylphosphino)dicyclopentane
Binap	(*R*) or (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	Benzyl group
Cy	Cyclohexyl
DCM	Dichloromethane

1,3-DCR	1,3-Dipolar cycloaddition reaction
ee	Enantiomeric excess
EWG	Electron-withdrawing group
Fesulphos	(R_p)-2-(*tert*-Butylsulfenyl)-1-(diphenylphosphino)ferrocene
FMO	Frontier molecular orbital
HetAr	Heteroaromatic group
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
Me-Du-Phos	[(–)-1,2-bis-(2*R*,5*R*)-2,5-dimethylphospholano]benzene
4 Å MS	4 Å molecular sieves
Naph	Naphthyl
NMM	*N*-methylmaleimide
NPM	*N*-phenylmaleimide
Penn-Phos	*P*,*P*′-1,2-phenylenebis(*endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1] heptane)
Ph-Box	2,2′-Isopropylidene-bis[(4*S*)-4-phenyl-2-oxazoline]
Ph-Dbphox	(*R*,*R*)-4,6-Dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)
PS	Polystyrene
PTC	Phase transfer catalysis
Py	Pyridine
Pinap	(*R*) or (*S*)-1-[2-(diphenylphosphino)-1-naphthyl]phthalazine
Quinap	(*R*) or (*S*)-1-[2-(diphenylphosphino)-1-naphthyl]isoquinoline
Segphos	(4,4′-Bi-1,3-benzodioxole)-5,5′-diyl-bis(diphenylphosphine)
Taniaphos	(R_p) 2-{(*R*)-(dimethylamino)-2-[(diphenylphosphino)phenyl]methyl}-1-(diphenylphosphino)ferrocene
*t*Bu-Box	2,2′-Isopropylidene-bis[(4*S*)-4-*tert*-butyl-2-oxazoline]
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl group
o-Tol	*o*-Tolyl (2-methylphenyl) group
TS	Transition state
ZINDO	Modified INDO (Intermediate neglect of the differential overlap) program. It is a semi-empirical molecular-orbital program for studying the spectroscopic properties a wide range of compounds, including organic and inorganic molecules, polymers, and organometallic complexes.

1 Introduction

The main challenge in asymmetric synthesis is to generate the maximum number of stereogenic centers in only one reaction step by employing the minimum amounts of the reagents. While searching for a perfect and tuneable catalyst able to promote a wide array of transformations [1], asymmetric catalysis was revealed as a powerful tool from the economic and synthetic point of view. These basic concepts, together with the continuous demand for enantiomerically enriched molecules, prompt organic chemists to develop and screen new catalytic systems. The most attractive transformations are electrocyclic reactions [2, 3] because they satisfy all these requirements. In

fact, the absolute configuration of several carbon atoms (up to four) can be established almost simultaneously. The 1,3-dipolar cycloaddition reaction (1,3-DCR) of azomethine ylides [4–15], generated from imino esters **I**, with electron-deficient alkenes **II** is an important and representative process, which allows the stereoselective synthesis of pyrrolidine or proline derivatives **III** (Scheme 1). These products **III** [16, 17] are very useful compounds in the synthesis of α-amino acids [16, 17], natural products [16, 17], pharmaceuticals [16–22], organocatalysts [23, 24], etc.



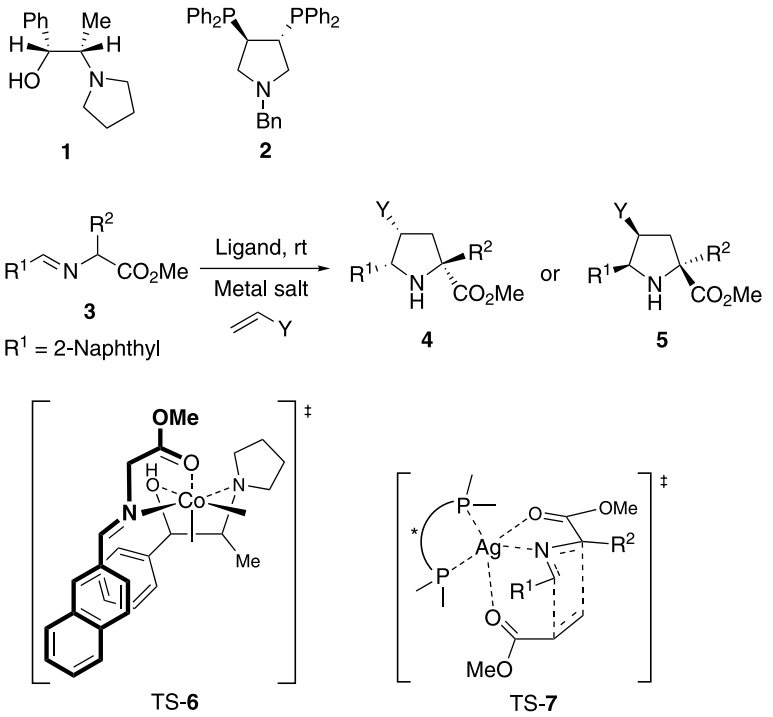
Scheme 1 General asymmetric 1,3-DCR of azomethine ylides

In this cycloaddition, the particular structure of the azomethine ylides promotes a characteristic frontier molecular orbital (FMO) controlled reactivity with alkenes [25], which can lead to the formation of four stereocenters. There are several procedures for generating azomethine ylides, but the metallation of imino esters **I** is the most widely used in organic chemistry [11, 12]. The benefits of the in situ preparation of metallo-azomethine dipoles from α-imino esters **I** in basic media, such as working at room temperature with a highly coordinated transition state and starting from easily available compounds, make this reaction very attractive (Scheme 1). The asymmetric version of this 1,3-dipolar cycloaddition reaction can be accomplished following different strategies [4–15]: (a) by bonding a chiral auxiliary in the imino (R^1) or in the electron-withdrawing group (EWG^1) of the dipole precursor **I**; (b) by attaching a chiral auxiliary in the EWG^2 of the alkene **II**; (c) by employing a chiral Lewis acid able to chelate one or both components **I** and **II**; (d) by lowering of the LUMO energy of the dipolarophile using organocatalysts; and (e) by using chiral bases as catalysts for the enolization of the imino ester. Focussing our analysis on the catalytic enantioselective 1,3-DCR of azomethine ylides, we will deal with the facets included in strategies (c), (d), and (e).

2
Chiral Lewis Acid-Catalyzed 1,3-DCR

Considering all of the previously mentioned advantages and the behavior of metallo-azomethine ylides, the catalytic enantioselective version was, undoubtedly, a very exciting area to explore. In a seminal work, Grigg and co-workers [26, 27] employed a stoichiometric amount of the catalytic system

ephedrine derivative **1**-Co(II) chloride in the reaction of the dipole precursor **3** with the dipolarophile (Y = CO_2Me, used as solvent) which led to an excellent ee in the case of the stereoisomer **4** with total *endo*-selectivity[1] (Scheme 2). However, the stoichiometric catalyst formed by bisphosphine **2**-AgOTf afforded its mirror image *endo*-**5**, albeit with low enantioselection [26, 27]. The high enantiomeric excesses obtained in these examples can be justified, presumably, by the formation of compact transition states TS-**6** and TS-**7**, respectively. Despite these attractive precedents, the first asymmetric catalytic 1,3-dipolar cycloaddition reaction, using substoichiometric amounts of a chiral metallic complex, remained unexplored until 2002 [28].



Scheme 2 Enantioselective 1,3-DCR using stoichiometric chiral metal complexes

2.1 Chiral Ag-Complexes

The pioneering work reported by Zhang's group [28] screened several bisphosphine ligands, such as Binap, Me-Duphos, Pennphos, and Bicp, with

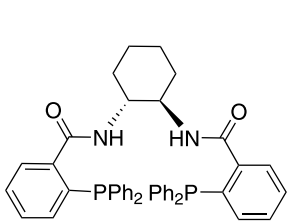
[1] The terms *endo* or *exo* refer to the approach of the dipolarophile with its electron-withdrawing group oriented toward the metal center or away from it, respectively. This nomenclature is independent of whether the reaction is or is not concerted

Table 1 1,3-DCR using stoichiometric amounts of chiral Co- and Ag-complexes

R^2	Y	Ligand	Metal salt	Yield (%)	Product[a] ee (%)
H	CO_2Me	**1**	$CoCl_2$	84	**4** (96)
Me	COMe	**2**	AgOTf	83	**5** (70)
Me	SO_2Ph	**2**	AgOTf	84	**5** (70)

[a] The *endo*:*exo* ratio was >98 : 2 in all of the transformations

silver acetate, which led to low enantioselectivities of the corresponding *endo*-cycloadducts **10** (Scheme 3). However, the reaction of the imino esters **3** and dimethyl maleate occurred with a promising good enantioselection (59% ee) when Trost's ligand **8** and AgOAc were employed. These data prompted the authors to design new ligands such as **9**, which incorporated an additional element of planar chirality (two ferrocene units) able to impart different steric and stereoelectronic properties on the product **10** (Scheme 3 and Table 2). The reaction operated mainly at 0 °C in relatively short reaction times (7 h) for the α-(arylimino)esters whilst 48 h were required for the α-(alkylimino)esters. The best results for the *endo*-adducts were obtained when dimethyl maleate was used as dipolarophile (Table 2). The reaction of the glycine imine **3** (R^1 = Ph, R^2 = H) was also performed with dimethyl fumarate (52% ee), NMM (79% ee), and *tert*-butyl acrylate (93% ee) (Table 2). The adducts **10** were formed in good yields and noticeable enantiomeric purity (up to 81% ee) in the reaction of dimethyl maleate and imino esters whose substituent R^1 was a cyclohexyl or an isopropyl group. In previous works, it has been pointed out that Michael-type addition re-



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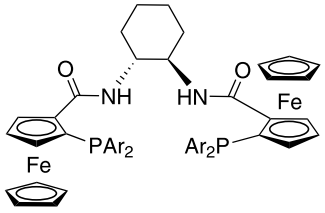
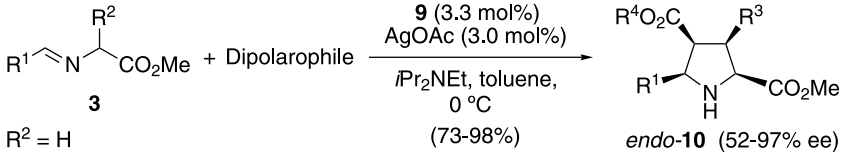


9 Ar = 3,5-dimethylphenyl



3

R^2 = H

endo-**10** (52-97% ee)

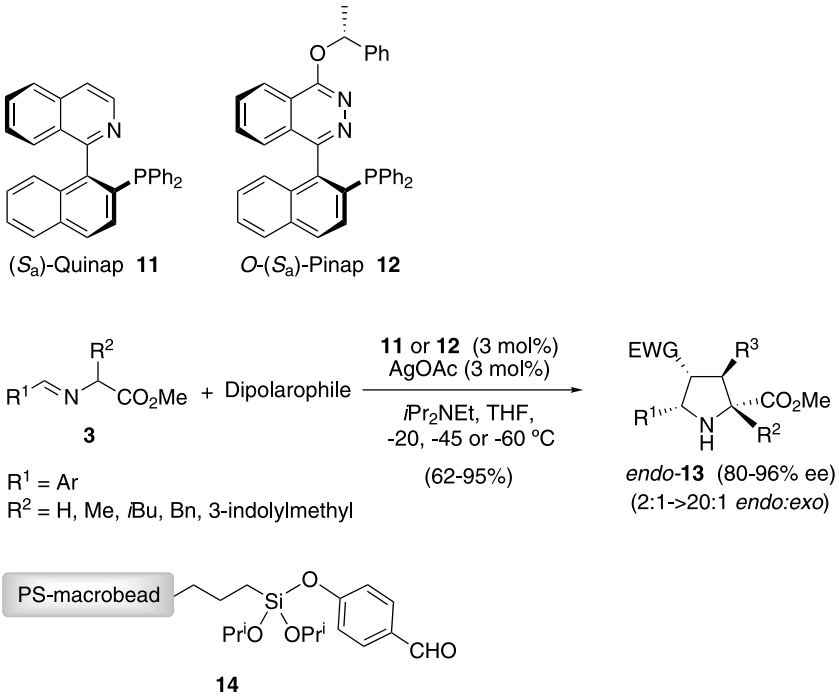
Scheme 3 Enantioselective 1,3-DCR using **9**-AgOAc complex

Table 2 Enantioselective 1,3-DCR between **3** and dipolarophiles using chiral **9**-AgOAc complex

R^1	Dipolarophile	Yield (%)	ee (%)
Ph	Methyl maleate	87	87
4-(NC)C_6H_4	Methyl maleate	90	86
2-Naph	Methyl maleate	98	97
*i*Pr	Methyl maleate	82	70
Cy	Methyl maleate	82	81
Ph	Methyl acrylate	90	60
Ph	*t*Butyl acrylate	85	93
Ph	Methyl fumarate	88	52
Ph	NMM	87	79

action of these dipolar precursors (R^1 = alkyl) onto electrophilic alkenes is the expected pathway and, normally, little cyclization occurred [29]. The *endo*:*exo* ratios were so high that, in most of the examples investigated, the *exo*-diastereomer was not even detected (no numerical data concerning the *endo*-diastereoselectivity was mentioned). In order to explain this *endo*-selectivity, the authors proposed an interaction of the silver metal cation with both the dipole and the dipolarophile generating an identical intermediate to TS-**7**.

Later Schreiber's group developed a versatile stepwise, three-component 1,3-DCR of azomethine ylides and electron-deficient olefins (Scheme 4) [30, 31]. Thus, the non-isolated imine **3**, obtained from the corresponding aldehyde and the α-amino acid alkyl ester, reacted with acrylates in the presence of a catalyst formed by ligand (S_a)-Quinap **11** (3 mol %) and AgOAc (3 mol %). The reaction was carried out at different temperatures according to the nature of both the imino ester and the dipolarophile. Thus, *tert*-butyl acrylate reacted with imino esters **3** (R^1 = Ph, R^2 = H) at –45 °C in 20 h, but –20 °C was the preferred temperature to promote the cycloadditions between *tert*-butyl acrylate with α-substituted imines **3** (R^1 = Ph, R^2 = Me, *i*Bu, Bn, 3-indolylmethyl) (Table 3). In the latter series, longer reaction times were required, for example, 1 d was employed in the reaction with the alanine derived 1,3-dipole, 2 d for the leucine and the phenylalanine derivatives, and 4 d were necessary for the tryptophan analogue **3** to achieve the corresponding cycloadduct *endo*-**13** in 47–98% yield. In addition, *tert*-butyl crotonate (Table 3) and *tert*-butyl cinnamate reacted with **3** (R^1 = Ph) at –20 °C giving compound *endo*-**13** with 84% ee and 81% ee, respectively. The main drawbacks of this alternative reaction was the high amounts of both AgOAc and the (S_a)-**11** ligand (10 mol % each) and the longer reaction times required. In all of the examples described, the *endo*-adduct **13** was obtained as the major diastereoisomer (from 2 : 1 to >20 : 1 *endo*:*exo* ratio) [30].



Scheme 4 Enantioselective 1,3-DCR using **11**- or **12**-AgOAc complexes

Table 3 Enantioselective 1,3-DCR between **3** and dipolarophiles using chiral **11**- or **12**-AgOAc complexes

R^1	R^2	R^3	Ligand	T (°C)	Dipolarophile	Yield (%)	ee[a] (%)
Ph	H	Me	**11**	–20	*t*Butyl crotonate	97	84
Ph	Me	H	**11**	–20	*t*Butyl acrylate	98	80
Ph	*i*Bu	H	**11**	–20	*t*Butyl acrylate	97	84
4-(NC)C_6H_4	H	H	**11**	–45	*t*Butyl acrylate	92	96
4-(NC)C_6H_4	H	H	**12**	–40	*t*Butyl acrylate	94	95

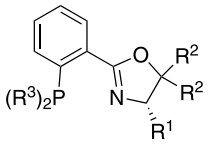
[a] In all of the examples the *endo*:*exo* diastereomeric ratio was >20 : 1

The above study also introduced the reaction of a supported aldehyde **14**, loaded onto alkyl-silyl derivatized 500–600 μm polystyrene macrobeads, with glycine methyl ester. The freshly generated imino ester reacted with *tert*-butyl acrylate at –45 °C for 40 h employing a 10 mol % of the catalytic mixture **11**-AgOAc. The *endo*-cycloadduct **13** (R^1 = Ph, R^2 = H, R^3 = H, EWG = CO_2tBu) was isolated, after cleavage with HF-Py and a TMSOEt quench, in 79% yield

with high diastereoselection (>20 : 1 *endo*:*exo* ratio) and good ee (90%). In spite of the operational advantages of this combinatorial transformation, the achieved results are equivalent to the non-supported reaction conditions, and isolation of cycloadduct *endo*-**13**, through the combinatorial sequence, required one more step than the analogous non-supported reaction [30].

The reaction shown in Scheme 4 was performed at –40 °C in order to test the catalytic activity of the complex formed by *O*-(S_a)-Pinap **12**-AgOAc [32]. Both chemical yield (94%) and ee (95%) (Table 3, entry 5) were equivalent to the results given by the complex (S_a)-Quinap **11**-AgOAc at similar temperatures. The advantage of the ligand **12** over the ligand **11** remained clear because (S_a)-Quinap (a rather expensive, commercially available chemical) was prepared in a six-step sequence including a resolution stage performed with a chiral palladium complex, whilst enantiomerically enriched ligand **12** was prepared in a three-step route and conveniently separated by crystallization or flash chromatography.

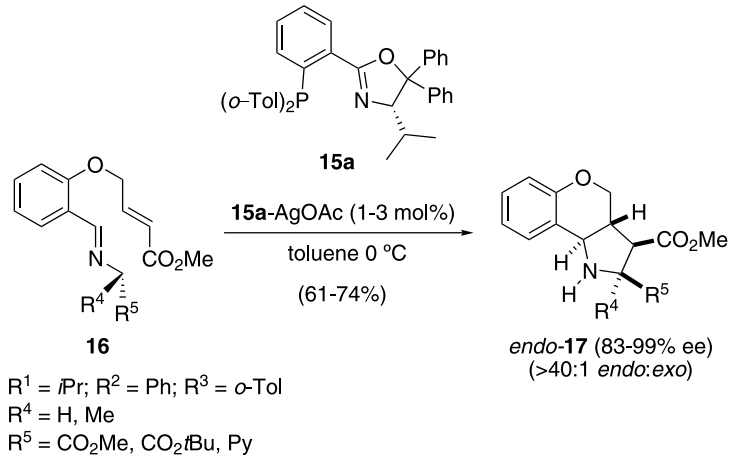
Lower enantioselections have been exhibited by the complexes formed by the couple AgOAc-Phox-ligands **15** (1–3 mol %) in the 1,3-DCR of azomethine ylides derived from imino esters **3** (R^1 = 2-naphthyl, R^2 = H) and methyl acrylate in the absence of a base. In general, the *endo*-products **10** were obtained as major stereoisomers (from 9 : 1 to >40 : 1 *endo*:*exo* ratio) in toluene at 0 °C for 5–9 h, the best enantioselectivities (65–67% ee) being achieved when ligand **15a** (R^1 = *i*Pr, R^2 = Ph, and R^3 = *o* – Tol) was employed [33]. Worth mentioning is the complete diastereocontrol and high enantio-discrimination detected during the intramolecular 1,3-DCR of the 1,2-disubstituted benzenes **16** catalyzed by the same complex **15a**-AgOAc (Scheme 5). In these examples, the reaction was performed at 0 °C as well, and took place in 6 h, acting the acetate ion as base. The framework of the optically pure tricyclic molecules *endo*-**17** (with undetermined absolute configuration) is a very interesting skeleton for the synthesis of many natural occurring alkaloids and biologically active products.



15

Fig. 1 Ligands **15**

Based on the above described processes, it is possible to conclude that the chiral Ag(I) complexes would act as catalysts, favoring the optimal HOMO-LUMO approach of both components, by coordinating strongly the 1,3-dipole and the dipolarophile through a relative weak interaction (see TS-**7**, Scheme 2).



Scheme 5 Enantioselective 1,3-DCR using Phox **15**-AgOAc complexes

Zhou's group employed ferrocenyloxazoline (*N*,*P*-ligands) **18**-AgOAc complexes in the 1,3-DCR of azomethine ylide precursors **3** and dimethyl maleate, without additional base being required [34–39]. The efficiency of this catalyst can be ascribed to its being a bifunctional catalyst [34–39], because the acetate anion itself acted as a base able to deprotonate the imino ester **3**. The reaction was very fast at –25 °C (3 h) in ether and gave good chemical yields and very high diastereo- and enantioselections of *endo*-**10** pyrrolidines (from 93 : 7 to >98 : 2 *endo*:*exo* ratios and from 88 to 98% ee, respectively) when the ligand **18a** (R = Bn, Ar = 4-$CF_3C_6H_4$) was employed (Scheme 6) [40]. Although the best enantioselectivity was achieved in the presence of dimethyl acrylate as the electron-deficient alkene, other dipolarophiles such as NMM (93% ee), *tert*-butyl acrylate (88% ee), and dimethyl fumarate (89% ee) also proved to be appropriate components for this asymmetric transformation.

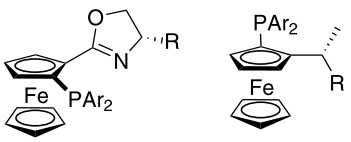
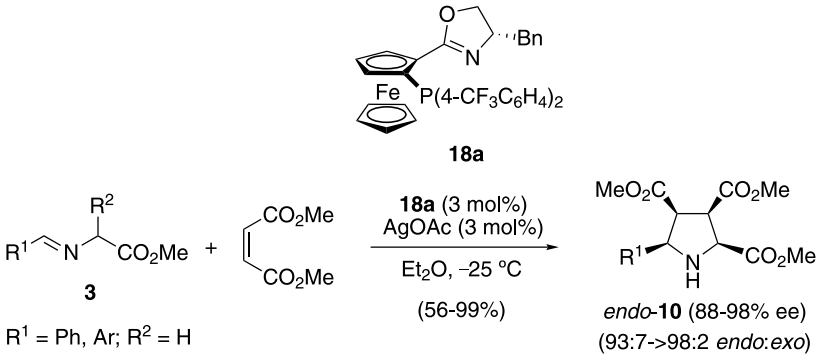


Fig. 2 Ligands **18** and **19**

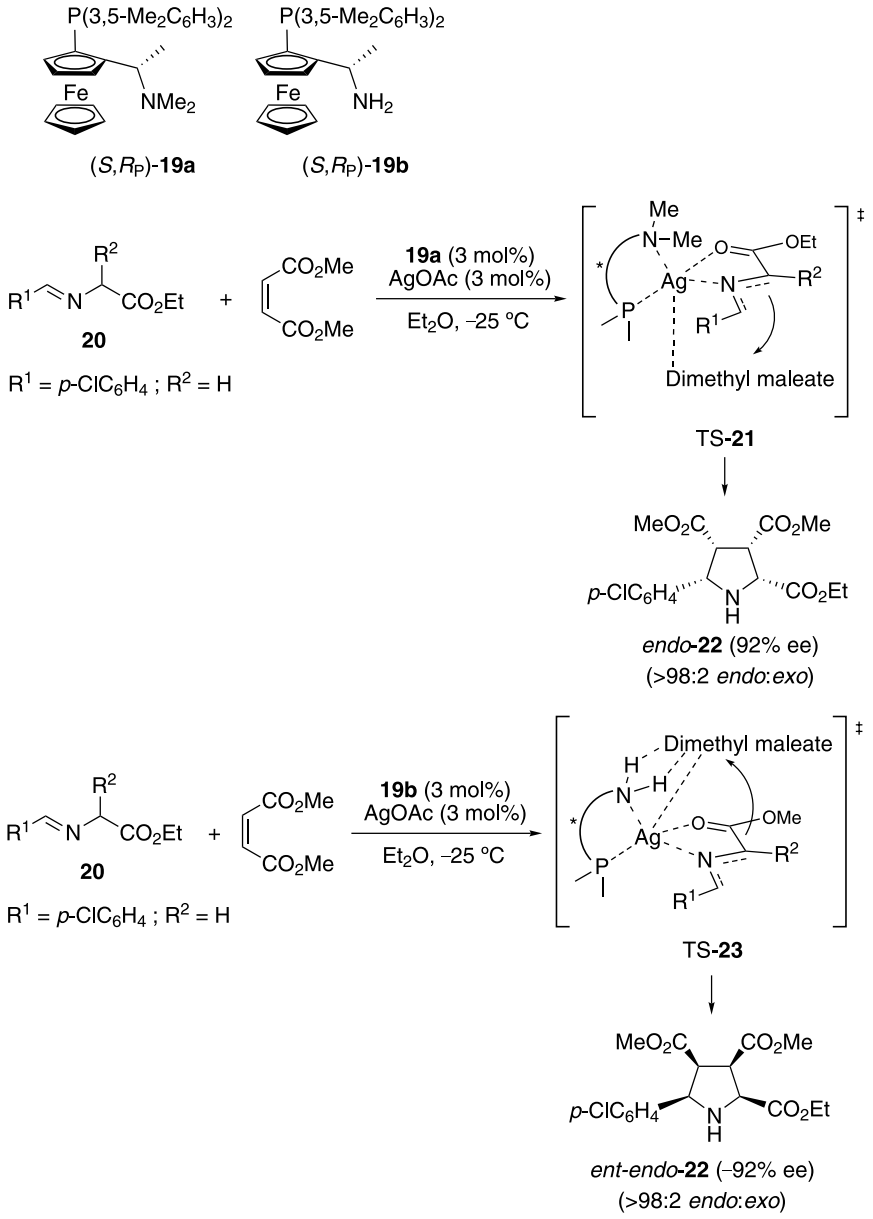
The same group further demonstrated how a very simple hydrogen bonding is enough to invert the enantioselection of the process [41]. The employed ligands were a different type of chiral ferrocenes (*S*,R_P)-**19**, which were combined with AgOAc. The proposed variation of the transition states TS-**21** and TS-**23**, supported by a computational study as well, is shown in Scheme 7.



Scheme 6 1,3-DCR catalyzed by chiral ligand **18a**

The carbonyl groups of the dipolarophile can be coordinated by the Ag cation of the (*S*,R_P)-**19b**-AgOAc complex and may form two hydrogen-bonding interactions with the NH_2 group (TS-**23**). However, the dimethylamino group of the complex (*S*,R_P)-**19a**-AgOAc cannot form these hydrogen bonds and the methyl groups would cause steric repulsion in TS-**21**. The proposed two different approaches could explain the experimentally observed opposite facial enantio-discrimination. Thus, when the *p*-chlorobenzaldehyde imine **20** was allowed to react with dimethyl maleate, under the reaction conditions described in the Scheme 6, it was deduced that the absence of hydrogen bonding in TS-**21** [(*S*,R_P)-**19a**-AgOAc complex] would give the pyrrolidine *endo*-**22** (92% ee and >98 : 2 *endo*:*exo* ratio, Scheme 7), whilst the TS-**23** [(*S*,R_P)-**19b**-AgOAc complex] would generate the corresponding adduct *ent*-*endo*-**22** (–92% ee and >98 : 2 *endo*:*exo* ratio, Scheme 7).

An important aspect, such as the recovery and reuse of the catalytic complex, has been recently communicated by our group. Usually, in an asymmetric transformation, the most important goal is the achievement of the highest ee and frequently no attention is paid to the chiral catalyst after the end of the reaction. The first example of using a very stable and recyclable catalyst, namely chiral (*R*)- or (*S*)-Binap **24**-$AgClO_4$ complexes (5 mol %), in the enantioselective 1,3-DCR of amino acid derived azomethine ylides and maleimides has been recently described [42]. The reactions were performed at room temperature, and proceeded in good yields with high *endo*-diastereo- and enantioselectivity, the catalytic chiral complex being recovered by simple filtration. The (R_a)- and (S_a)-Binap **24**-$AgClO_4$, formed by mixing equimolar amounts of both chiral ligand and $AgClO_4$, were very insoluble in toluene and efficiently catalyzed the 1,3-DCR of azomethine ylides derived from **3** and NMM, at room temperature in 17 h, to yield *endo*-adducts **25** (from 95 : 5 to >98 : 2 *endo*:*exo* ratio, and from 80 to >99% ee, Scheme 8 and Table 4) [42]. The same catalyst (S_a)-Binap **24**-$AgClO_4$ (89–92% recovery yield) was able to catalyze efficiently five batches of new reactions without



Scheme 7 1,3-DCR using chiral ligands **19a** and **b**

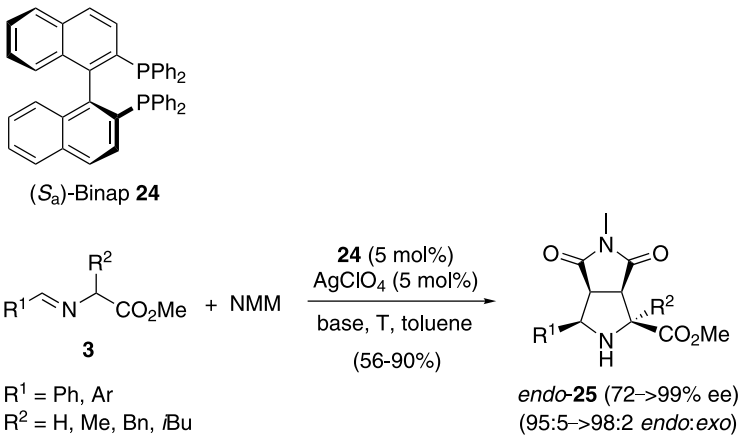
significant loss of enantioselectivity. Moreover, these complexes, (R_a)- (S_a)-**24**-$AgClO_4$, were very stable to light exposure and their isolation, storage and manipulation did not require any especial care. Once more, this type of cycloaddition demonstrated its sensitivity to the electronic nature and the

Table 4 Enantioselective 1,3-DCR between **3** and NMM using chiral, recyclable (S_a)-Binap **24**-AgOAc complex

R^1	R^2	*T* (°C)	Yield (%)	*endo*:*exo*	ee (%)
Ph	H	25	90	>98 : 2	>99
2-naphthyl	H	25	89	>98 : 2	>99
4-Me-C_6H_4	H	25	88	>98 : 2	88
4-Me-C_6H_4	H	0[a]	88	>98 : 2	>99
Ph	Bn	25	56	>98 : 2	98
Ph	*i*Bu	25	87	>98 : 2	74

[a] Reaction performed with DBU (5 mol %)

bulkiness of the substituents attached to the α-position of the imino ester **3**. Thus, dipoles derived from alanine (R^2 = Me), phenylalanine (R^2 = Bn), or leucine (R^2 = *i*Bu), were essayed and led to *endo*-pyrrolidines **25** (>98 : 2 *endo*:*exo* ratio in all cases) in good yield (56–81%) and acceptable enantioselection (from 72 to 98% ee) (Scheme 8). Initially, the reaction was tested at room temperature using Et_3N (5 mol %) as base, but in some cases the ee's could be improved by using DBU as base at 0 °C or even –20 °C.



Scheme 8 1,3-DCR catalyzed by the complex (S_a)-Binap **24**-$AgClO_4$

Several stable silver triflate complexes with (*R*)-Binap as ligand have been isolated at very low temperatures, used in aldol reactions and characterized by X-ray diffraction analysis by Yamamoto's group [43]. However, at room temperature, the binap-$AgClO_4$ complexes **26** and **27** could not be differentiated by ^{31}P NMR spectroscopy and could not be characterized by X-ray diffraction analysis [42]. The 1 : 1 complex (S_a)-**26** was obtained in quantitative yield from Binap and $AgClO_4$ and further characterized by ESI-MS

experiments showing an $M^+ + 1$ signal at 731 and a tiny one at 1353. Curiously, the same MS experiments revealed a peak at 1353 and a very small one at 731 for the complex (S_a)-**27** (Fig. 3), generated by mixing ligand:silver salt in a 2 : 1 ratio.

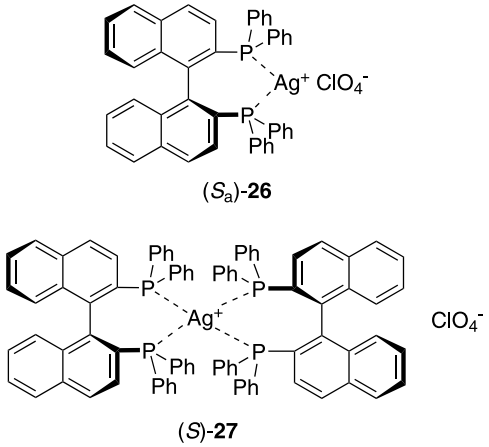


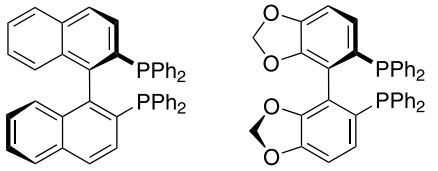
Fig. 3 Ag(I) complexes **26** and **27**

Considering the reported Ag(I)-catalyzed enantioselective reactions, one can conclude that not one chiral complex so far, is able to induce excellent enantioselectivity independently of structure of the dipole and the dipolarophile employed. This is indeed a difficult task and the most efficient and general chiral Ag(I)-catalyst is the (S_a)-Quinap **11**-AgOAc at different temperatures [31], but the highest ee reported so far corresponded to the reaction of **3** with NMM catalyzed by (S_a)-**24**-$AgClO_4$ [42]. As common features, all the Ag(I)-complexes are used in 3–5 mol % amounts, (although a few examples worked with a 1 mol % of catalyst), yielding mainly pure *endo*-adducts **10** (52–98% ee, Schemes 3, and 6) [29, 40, 41], **13** (80–96% ee, Scheme 4), **17** (83–99% ee, Scheme 5) [33], and **25** (72–>99% ee, Scheme 8) [42] or adducts slightly contaminated by the corresponding *exo*-adduct. This result can be a consequence of the high affinity of the silver cation toward the nitrogen or the oxygen atoms, facilitating the approach of the two components in a highly ordered transition state. The idea of recovering the unaltered catalysts and their further reuse will make this process more attractive even in larger-scale production.

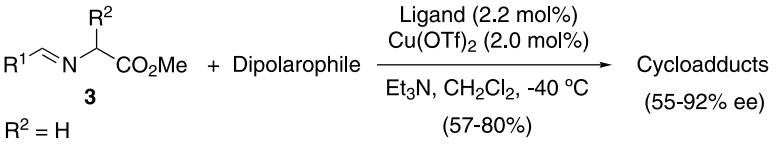
2.2 Chiral Cu-Complexes

In general, with the exception of the Binap **24**-$AgClO_4$ complex, it has been shown that, for the catalytic enantioselective 1,3-DCR, chiral bis-phosphine

ligands form more efficient complexes with $Cu(OTf)_2$ than with silver acetate. Komatsu's group found a reverse *exo*-selectivity using chiral bisphosphine-$Cu(OTf)_2$ at −40 °C for long reaction times (1–3 d) [44]. In most of the cases, the *exo*:*endo* ratio exceeded 95 : 5 using *N*-phenylmaleimide (NPM), the higher enantioselection being achieved with the catalytic systems formed by (R_a)-Binap **24**-$Cu(OTf)_2$ or (R_a)-Segphos **28**-$Cu(OTf)_2$. With other dipolarophiles, such as dimethyl fumarate or fumaronitrile, the *endo*-adduct (e.g. **29**) was formed in higher proportion (Scheme 9 and Table 5).

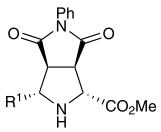
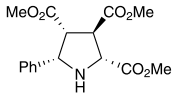


(R_a)-Binap **24** (R_a)-Segphos **28**

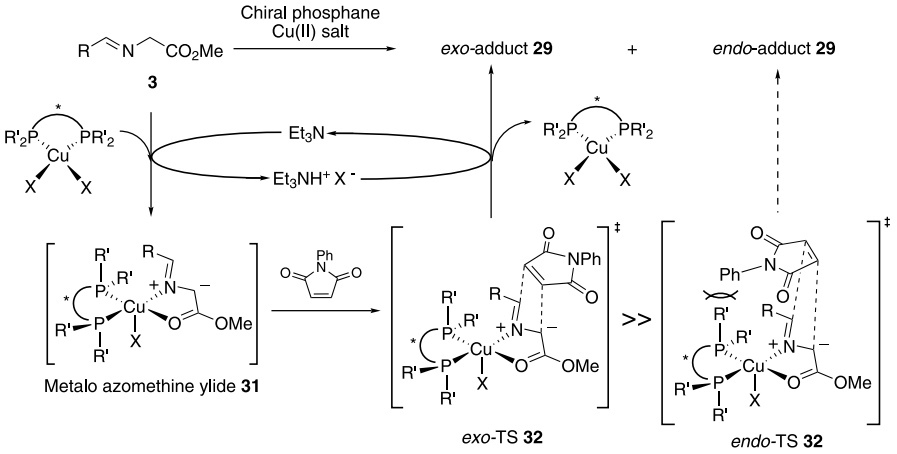


Scheme 9 1,3-DCR with catalyst formed with $Cu(OTf)_2$ and ligands **24** or **28**

Table 5 Enantioselective 1,3-DCR between **3** and dipolarophiles using chiral **24**- or **28**-$Cu(OTf)_2$ complexes

R^1	Ligand	Dipolarophile	Adduct	*endo*:*exo*	ee_{exo} (%)
4-(MeO)C_6H_4	**24**	NPM		<5 : 95	87
Ph	**28**	NPM		15 : 85	72
			83-78% *exo*-**29**		
Ph	**24**	dimethyl fumarate		64 : 36	81
			endo-**30**		

The authors proposed a plausible mechanism for the cycloaddition reaction and for the obtained diastereoselection (Scheme 10). The azomethine ylide-Cu complex **31** would be generated under basic conditions, reacting with NPM according to the *exo*-approach TS-**32**, in order to diminish the steric interactions caused in the *endo*-transition state **32** by the phosphorous



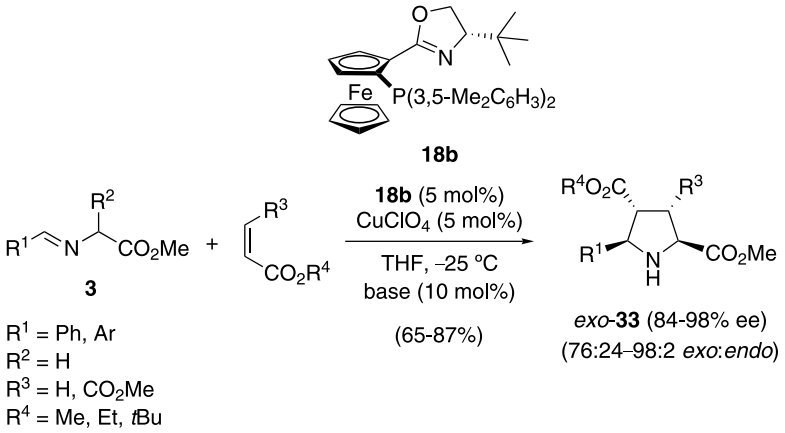
Scheme 10 Proposed mechanism for the *exo*-selectivity obtained using Cu(II) complexes

substituents. This hypothesis was also supported by calculations performed using the ZINDO method[2].

As a preliminary conclusion of these studies involving chiral Cu(II) complexes, the *endo*- and *exo*-selectivity can be controlled to some extend by the nature of the chiral metal complexes and by the substrates employed in the reaction. The cycloadducts were obtained with good to moderate diastereo- and enantioselectivities, but the presence of undesirable mixtures of *endo*:*exo* cycloadducts at the end of the reaction are unavoidable.

In addition to Cu(II), Cu(I) complexes also have been employed as catalysts in the enantioselective 1,3-DCR. The catalytic complexes formed by ligand **9** (Ar = Ph) or by ligand (S_a)-Binap **24** and CuOAc afforded moderate to good or very low enantioselectivities, respectively. However, ligand **18b** (R = *t*Bu, Ar = 3,5-$Me_2C_6H_3$) and $CuClO_4$ (both in 5 mol % loading) afforded high enantioselections (from 89 to 98% ee) of the corresponding *exo*-adduct **33** (from 76 : 24 to 98 : 2 *exo*:*endo* ratio) in THF at –25 °C (Scheme 11) [45]. The effect of the R^2 substituent in the dipole precursor **3** under the standard reaction conditions has not been reported yet. For imino esters **3**, bearing an electron-withdrawing substituent on the aryl group, the reactions with acrylates or maleates proceeded smoothly in the presence of Et_3N as base (10 mol %) for 20 h. However, for substrates **3** having no substituents or an electron-donating group, such as methyl or methoxy groups on the aryl unit the reaction became extremely slow. In these cases, the employment of DBU led to the desired *exo*-adducts **33** in high yields and very good enantioselectivities (61–84% yield and 84–91% ee). Independently of the base employed

[2] ZINDO: Modified INDO (intermediate neglect of the differential overlap) program. It is a semiempirical molecular orbital program for studying the spectroscopic properties of a wide range of compounds, such as organic and inorganic molecules, polymers, and organometallic complexes.

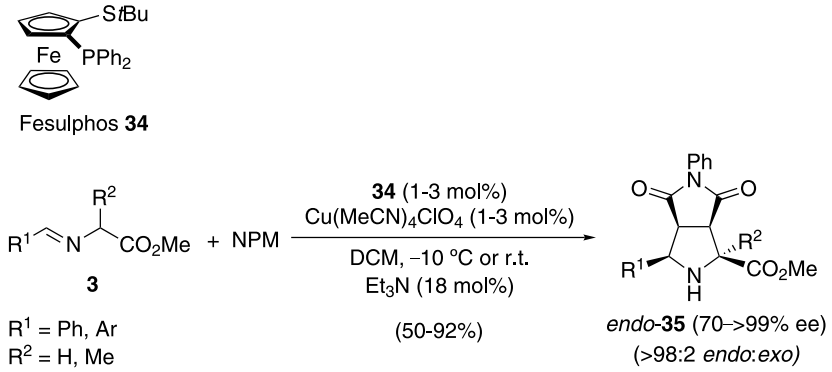


Scheme 11 1,3-DCR of azomethine ylide precursors and acrylates or maleates catalyzed by **18b**-Cu(I) salts

in this last reaction, the *exo*:*endo* ratios were higher than the ratios observed when ligands **24** and **28** with Cu(II) triflate were employed (see Scheme 9 and Table 5). The authors proposed the existence of a first intermediate 1,3-dipole-chiral Cu(I) complex (18 electrons), whose substituents underwent steric and electronic repulsion with the electron-withdrawing groups of the dipolarophile. This fact may contribute to the good *exo*-selectivities and the inhibition of the *endo*-approach [45].

The efficiency of the chiral Cu(I)-complexes has also been demonstrated by Carretero's group using the chiral ligand Fesulphos **34**, showing exceptional levels of diastereo- and enantioselectivity [46, 47]. Initially, the copper salt $Cu(MeCN)_4ClO_4$ afforded complete stereocontrol in the 1,3-DCR of the imino ester **3** ($R^1 = Ph$, $R^2 = H$) and NPM, at room temperature in 15 min, leading to the *endo* cycloadduct (>98 : 2 *endo*:*exo* ratio) with more than 99% ee. This ee is the highest reported so far for the Cu(I)-catalyzed enantioselective [3 + 2] cycloaddition reaction (Scheme 12) [46, 47]. The same reaction was also studied at room temperature under the catalysis of **29**-AgOAc or **29**-$AgClO_4$, affording in both cases similar *endo*-selectivity (>98 : 2 *endo*:*exo* ratio) and enantioselectivity (89 and 86% ee, respectively). Aldimines **3** (with $R^1 = Ar$) reacted very fast with NPM (15–60 min) affording very high enantioselections of the *endo*-adducts **30** (from 70 to >99% ee), especially when the reaction was performed at –10 °C and using a 1 mol % of catalyst loading. The substitution of a hydrogen atom by a methyl group in R^2 furnished slightly lower enantioselectivities (80–92% ee) of the *endo*-product **30**, but in these examples higher reaction times and higher catalyst loadings (3 mol %) were required (Scheme 12) [46, 47].

The scope of this last process was surveyed with the *N*-benzylideneglycinate **3** ($R^1 = Ph$, $R^2 = H$) with symmetrically substituted dipolarophiles



Scheme 12 1,3-DCR o catalyzed by Fesulphos **34**-Cu(I) complex

as dimethyl maleate, dimethyl fumarate, and fumaronitrile. Temperature, solvent, base, catalysts, and Cu(I) or Ag(I) salts were the most important parameters evaluated in this study [47]. The reaction with dimethyl maleate in DCM afforded higher *exo*-selective (*exo*-**36**) than the reaction run with NPM when Fesulphos **34**-Cu(I) complex was essayed. The stereoselectivity of this reaction proved to be highly solvent-dependent, thus, in THF or toluene the *endo*:*exo* ratio of the adduct **36** decreased dramatically and in some examples the *exo* diastereoisomer is the major product. Under analogous reaction conditions, the employment of a Fesulphos **34**-AgOAc complex instead (3 mol %), even in toluene as solvent, at –10 °C, led to good *endo*-selectivities (>98 : 2 *endo*:*exo* ratio) but the enantioselectivity was significantly lower (66–77% ee) than that obtained in the Cu(I)-mediated processes (93–94% ee, Fig. 4) [47]. Dimethyl fumarate showed higher reactivity and *endo*-selectivity (90 : 10 *endo* **37**:*exo* **37** ratio) in THF at –10 °C, affording, after recrystallization, the compound *endo*-**37** in practically enantiopure form (> 99% ee, Fig. 4). A very different stereochemical outcome was found in the reaction with fumaronitrile. This dipolarophile was quite reactive and the reaction performed in THF at –30 °C afforded the highest (20 : 80) *endo*-**38**:*exo*-**38** ratio with a 76% ee determined for the major isomer *exo*-**38** (Fig. 4). Note that in all reactions the stereochemistry of the olefin was maintained, for example the *cis*-stereochemistry of dimethyl maleate was transferred to adducts **36** and **40**, whilst the *trans*-stereochemistry of methyl fumarate, fumaronitrile, and β-nitrostyrene was transferred to adducts **37**, **38**, and **42**, respectively.

The efficacy of the Fesulphos **34**-Cu(I) catalyst (3 mol %) in promoting enantioselective dipolar cycloadditions was also observed for monoactivated electrophilic alkenes, such as methyl acrylate, 2-butenolide, methacrolein, and for β-nitrostyrene. The 1,3-DCR of precursors **3** with methyl acrylate, in THF at room temperature, gave a 75 : 25 *endo*:*exo* ratio including a 95% ee for the *endo*-**39** cycloadduct. The α,β-unsaturated lactone 2-butenolide was used for the first time as a dipolarophile furnishing the *endo*-product **40**

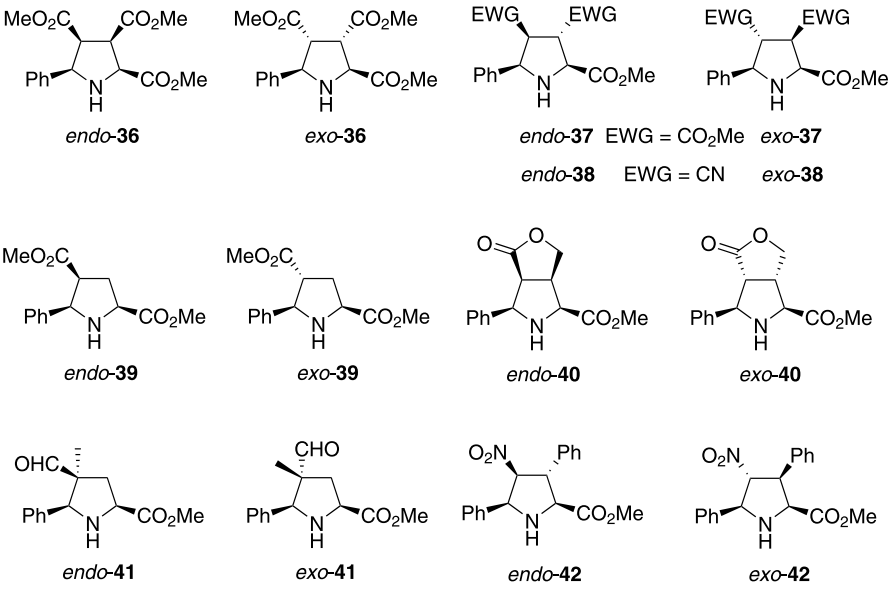
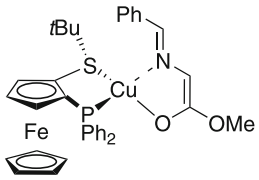


Fig. 4 Products of the 1,3-DCR of azomethine ylide precursors with symmetrical and non-symmetrical dipolarophiles catalyzed by Fesulphos **34**-Cu(I) complex

as the major isomer (60 : 40 *endo*:*exo* ratio) following the analogous reaction conditions described in the 1,3-DCR performed with methyl acrylate. The heretofore unexplored methacrolein as component of the 1,3-DCR using azomethine ylides offered excellent diastereoselectivities (>98 : 2 *endo*:*exo* ratio) but the resulting product *endo*-**41** was obtained only in 55% yield and 41% ee (Fig. 4). The importance of pyrrolidines bearing a nitro group at C-4 as potent inhibitors of the enzymes involved in the hepatic melanoma metastasis [47] encouraged the authors to develop the study of nitroalkenes in the catalytic enantioselective 1,3-DCR with **3** ($R^1 = Ph$, $R^2 = H$). The best *exo*-selectivity (95 : 5) for compound **42** was achieved working at −10 °C, in THF, and employing a 3 mol % loading of the catalyst (Fig. 4). The cycloadduct *exo*-**42** was obtained in 61% yield and high enantioselectivity (94% ee).

Based on NMR analysis and on the X-ray structure of different Fesulphos-Cu(I) complexes, the authors [47] proposed an intermediate complex **43** (Fig. 5). The distorted tetrahedral arrangement of all the ligands involved in the transformation exhibited very weak interactions with the *tert*-butyl group. The approach of the dipolarophile would avoid the interaction with this bulky group, which could explain the high enantioselectivity observed with most of the dipolarophiles. Several computational studies on the Cu- and Ag-catalytic complexes with azomethine ylides revealed that the P–Cu and S–Cu bond distances are significantly shorter than the corresponding P–Ag or S–Ag distances. Therefore, Cu-complexes should generate a more compact



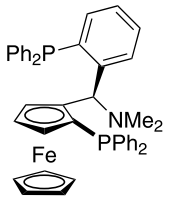
43

Fig. 5 Postulated pseudo-tetrahedral intermediate structure **43** for Fesulphos **34**-Cu(I)-dipole complex

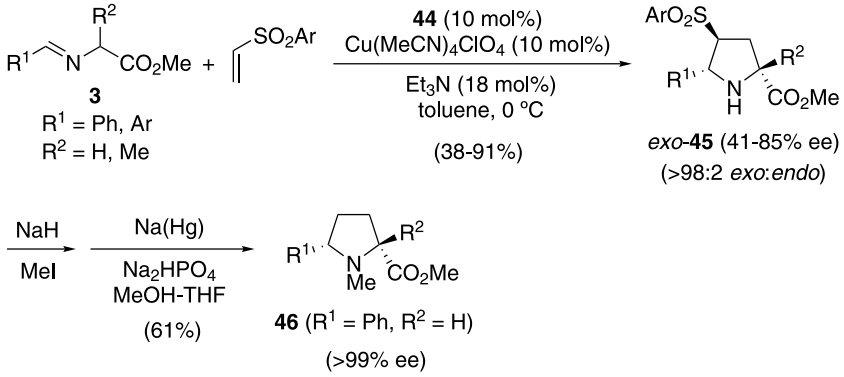
TS and the effect of the closer *tert*-butyl group would be more important. The high *endo*-selectivity observed in general was supported by energy calculations of the *exo*- and *endo*-TS. The *endo*-TS were lower in energy than their *exo*-analogues [47]. The computational analysis also predicted a probable concerted process when maleimides are involved in the 1,3-DCR, while a stepwise mechanism can be postulated for the other dipolarophiles, such as acrylates, fumarates, maleates, nitroalkenes, etc. In these last examples, the electrostatic interactions seem to be the responsible of the experimentally observed *endo*-selectivity.

In contrast to most of the chiral catalysts reported to date, the Fesulphos **34**-Cu(I) complex exhibited a broad scope with regard to the dipolarophiles and substituents attached to the dipole precursor **3**. The *endo*:*exo* selectivity showed a high dependence on the dipolarophile substitution, the regiocontrol in all of the cases was excellent, that means exclusive attack of the carbon α- to the ester in the dipole occurred onto the electron-poor β-position of the unsaturated alkene.

The synthesis of enantiomerically enriched 2,5-disubstituted pyrrolidines **45** has been optimized by the employment of a catalytic enantioselective 1,3-DCR of imino esters **3** and vinyl sulfones as the key step [48, 49]. Based on the chemical versatility of the sulfonyl group it was possible to run the catalytic asymmetric transformation using Taniaphos **44**-Cu(MeCN)$_4$ClO$_4$ complex (10 mol %) followed by a reductive desulfonylation [50] step under mild reaction conditions (Scheme 13). Following these two steps and corresponding purifications, the enantiomeric purity was increased to 99% for the final *N*-methylproline derivative **46**. The process was also sensitive to the presence of α-substituents on the dipole. The alanine derivative **3** (R^1 = Ph, R^2 = Me) gave an 80% ee of the *exo*-cycloadduct **45**, but the chemical yield was very low (38%). The aryl substituent of the sulfone did not affect the enantioselection of the process unless a nitrogen atom be present in the aromatic moiety (pyridine, *N*,*N*-dimethylamino group, etc). In general, it can be considered that this 1,3-DCR is widely general for glycinates regardless of the substitution at the aromatic ring of both the sulfonyl and imino groups, but the reaction became slower when a precursor of the alanine derivative **3** (R^2 = Me) was employed as substrate. The reaction was not successful when allenyl phenyl



Taniaphos **44**



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

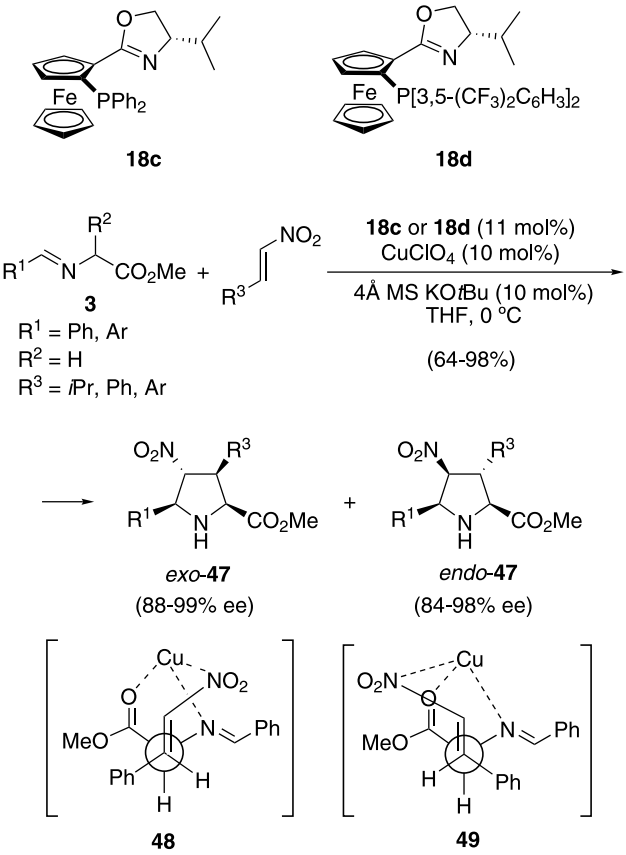
exo-**45** (41-85% ee)
(>98:2 *exo*:*endo*)

46 (R^1 = Ph, R^2 = H)
(>99% ee)

Scheme 13 1,3-DCR of azomethine ylide precursors with aryl vinyl sulfones catalyzed by Taniaphos **44**-Cu(I) complex

sulfone or propenyl phenyl sulfones were employed as dipolarophiles. In the overall transformation the aryl vinyl sulfone acted elegantly as an ethylene synthetic equivalent.

With respect to the 1,3-DCR involving nitroalkenes as dipolarophiles, the first catalytic enantioselective version was previously reported by Hou's group employing ligands **18c** (R = *i*Pr, Ar = Ph) or **18d** [R = *i*Pr, Ar = 3,5-$(CF_3)_2C_6H_3$] and Cu(I) salts and infrequently used additives such as 4 Å MS at 0 °C (Scheme 14) [51]. In this report, a high yield of either *exo*-**47** or *endo*-**47** adducts was achieved with excellent enantioselectivity by using electron-rich or electron-deficient aryl groups on the phosphorous atom of the chiral *P*,*N*-ferrocene ligands, respectively. The *exo*-adducts **47** were formed (from 86 : 14 to >98 : 2 *endo*:*exo* ratio and 88–99% ee) when ligand **18c** was employed whilst compound *endo*-**47** was the major stereoisomer generated (from 30 : 70 to 6 : 94 *exo*:*endo* ratio and 84–98% ee) when ligand **18d** was introduced in the Cu(I) coordination sphere [51]. Computational studies of the complexation models indicated two staggered intermediate complexes **48** and **49** for the *exo*- and *endo*-adducts **47**. In both aggregates, the nitro group, as a good coordinating element, remained very close to the copper atom. The two intermediate complexes **48** and **48** (Scheme 14) were also the most stable structures introducing the corresponding chiral ligand in the cop-

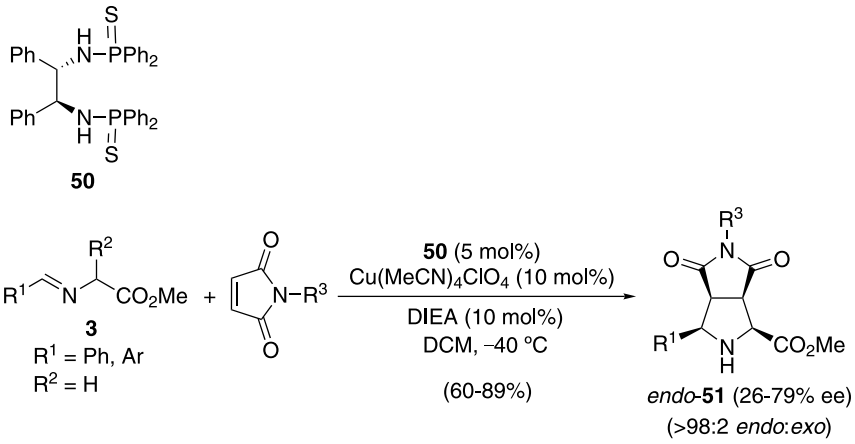


Scheme 14 1,3-DCR of azomethine ylide precursors with nitroalkenes catalyzed by complex **18c** or **18d**-Cu(I)

per coordination sphere. The results point to a new possibility to switch the stereoselectivity of the reaction by varying the electronic properties of the ligands, also called fine-tuned catalyst strategy.

Chiral bisthiophosphoramide **50** was not found to be a fairly effective ligand for Cu(I)-promoted 1,3-DCR of imines **3** and maleimides [52]. The *endo*-selectivity achieved was very high (>98 : 2 *endo*:*exo* ratio in all of the examples cited), but the enantioselection was moderate affording products **51** with ee ranging from 26 to 79%. The reaction was performed in DCM at –40 °C using a 5 mol % of catalyst loading (Scheme 15). In spite of similar enantioselectivities resulting from the use of **50**-Cu(I) complexes or **50**-Ag(I) complexes, the chemical yield obtained in the Cu(I)-catalyzed process was two times higher than the yield obtained when Ag(I) complexes were employed [52].

The Cu(I)-complexes are, in general, more versatile than Cu(II)-complexes and can be used for reaction of in situ-generated metallo-dipoles with a large

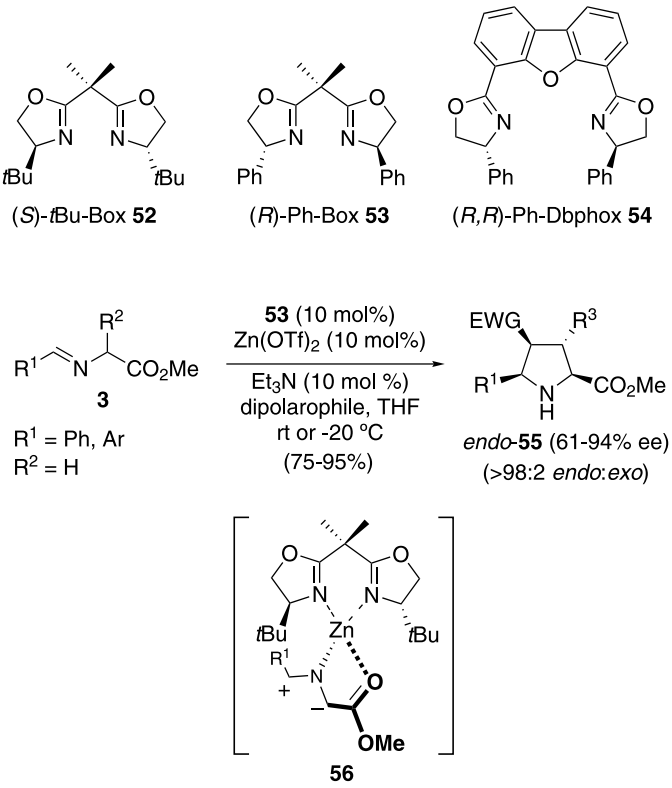


Scheme 15 1,3-DCR of azomethine ylide precursors with maleimides catalyzed by complex **50**-Cu(I)

number of dipolarophiles. One of the advantages of using Cu(I) versus Cu(II)-chelates is that control of diastereoselectivity and enantioselectivity is much more efficient. In fact, only one example of Cu(II)-catalyzed 1,3-DCR has been reported, while six detailed articles dealing with Cu(I)-based catalysts have been published so far. The most efficient and less structure-dependent Cu catalyst in the literature, is Fesulphos **34**-Cu(MeCN)$_4$ClO$_4$ [45–48].

2.3 Chiral Zn-Complexes

Chiral Zn(II)-complexes have been employed in the catalytic enantioselective 1,3-DCR, albeit to a lesser extent than the previously mentioned Ag(I)- and Cu(I)-catalysts. Jørgensen's group demonstrated than chiral bis-oxazolines **52–54** were suitable ligands in the standard 1,3-dipolar cycloaddition reaction of azomethine ylides and electrophilic alkenes when zinc(II) triflate, rather than copper(II) triflate, was used as Lewis acid [53]. The reaction between the imino ester **3** with several dipolarophiles occurred at room temperature or as low as –20 °C, stirring overnight, with excellent diastereoselectivity (*endo*-products **55** were exclusively formed with >98 : 2 *endo*:*exo* ratio), in very good chemical yields and very good ee (61–94%). In addition, an improvement of the enantioselectivity was observed when the reaction proceeded at –20 °C (Scheme 16 and Table 6). The catalyst charge employed in this reaction is sensibly higher than the catalyst amounts employed in the cases discussed above. These reaction conditions were independent of the quantity of base used and were very sensitive to the bulkiness of the substituents anchored to the dipolarophile. Based on the absolute configuration of the *N*-tosylated adducts derived from **55** (determined by X-ray analysis), the authors pro-



Scheme 16 1,3-DCR of azomethine ylide precursors with dipolarophiles catalyzed by complex **53**-Zn(II)

Table 6 Results of the catalytic enantioselective 1,3-DCR catalyzed by **53**-Zn(II) complex

R^1	R^3	*T* (°C)	Dipolarophile	Yield (%)	ee (%)
Ph	H	0	Methyl acrylate	95	78
4-BrC_6H_4	H	–20	Methyl acrylate	89	94
2-Naph	H	–20	Methyl acrylate	84	91
Ph	CO_2Me	–20	Dimethyl fumarate	78	76
2-Naph	CO_2Me	0	Dimethyl fumarate	84	90

posed an intermediate **56** where the azomethine ylide would coordinate with the Zn(II)-*t*Bu-Box catalyst forming an 18-electron complex with a tetrahedral arrangement of the ligand around the metal center (Scheme 15 and Table 5) [53].

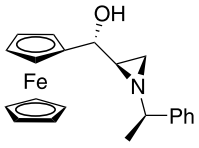


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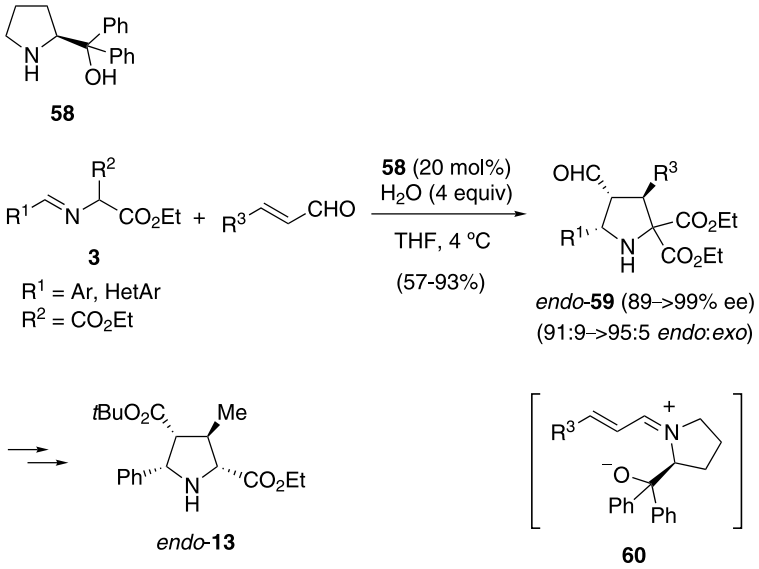
Fig. 6 Chiral aziridino alcohol **57**

Later on, Garner's group reported a new easily obtainable chiral aziridino alcohol **57** (Fig. 6), which was combined with $Zn(OTf)_2$ to prepare a catalytic complex tested in the 1,3-DCR [54]. The reaction conditions were exactly the same as the parameters described in Scheme 16 for the Box-Phox ligands **52–54** (10 mol %). These results did not improve the enantioselections obtained with **53**-Zn(II) complex, but in some examples both type of complexes gave very similar ee of the same *endo*-cycloadduct **55** (up to 95% ee). The absolute sense of asymmetric induction appeared to be again dipolarophile-dependent. The authors also suggested the formation of an intermediate complex similar to **56** by replacing the two coordinative nitrogen atoms of the chiral ligand by the nitrogen and the oxygen atoms of **57** [54].

3
Organocatalyzed 1,3-DCR

The rapid growing of asymmetric organocatalysis [23, 24] has recently covered the 1,3-DCR involving special azomethine ylides **3** and conjugated aldehydes. Based on the pioneering work of McMillan's group on 1,3-DCR using nitrones [55], the optimal organocatalyst **58** was found, after multiple tests including other different ligands and reaction conditions, as the most suitable molecule to activate the aldehyde as iminium ion **60** [56]. The presence of the hydroxy group in **58** was crucial to achieve high enantioselections; presumably, under these reaction conditions the electronic attraction of the alcoholate to the dipole favored a much more compact TS. The reactions succeeded when the precursor dipole was the imine derived from diethyl malonate because a spontaneous 1,2-prototropic shift (from the α-carbon to nitrogen) occurred without the presence of a base. These processes took place slowly at 4 °C for 3 d with high diastereo- (from 91 : 9 to >95 : 5 *endo*:*exo* ratio) and enantioselectivity (from 85 to >99% ee). The corresponding *endo*-adducts **59** were obtained in good chemical yields (57–93) (Scheme 17) [56]. In spite of the excellent results achieved, there are important structural and starting material restrictions. For example, exclusively α,β-unsaturated aldehydes can be employed as dipolarophiles so far and the effect of other substituents at the α-position cannot be studied. In addition, the aryl moiety is the unique modifiable part of the dipole, three stereogenic centers (in-

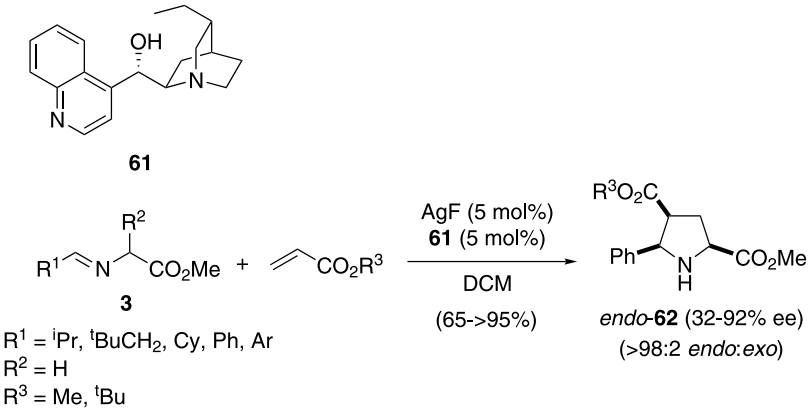


Scheme 17 Enantioselective 1,3-DCR of azomethine ylide precursors **3** with conjugated aldehydes mediated by organocatalyst **58**

stead of four) can be generated, and the amounts of the catalyst are rather high (20 mol %) while lower amounts caused a drop of the enantioselection. The authors justified the utility of this reaction in the synthesis of a proline derivative *endo*-**13** (EWG = CO_2tBu, R^1 = Ph, R^2 = H, and R^3 = Me) in which the additional fourth stereocenter was generated through standard chemical transformations. In fact, this could not be considered an advantage because more than five steps are required to obtain product *endo*-**13**, when as has been described in the previous sections, only one enantioselective step would be necessary to prepare this compound.

4 Chiral Bases

Another different approach for carrying out the enantioselective 1,3-DCR involves the addition of a chiral base in substoichiometric amount. Many cinchonine and cinchonidine derivatives as well as silver salts were essayed. The best conversions and more reproducible results were obtained when employing silver fluoride and the highest ee resulted in the reactions performed with chiral base **61** (Scheme 18) [57]. The reaction between *N*-alkylidene glycine esters **3** and *tert*-butyl acrylate catalyzed by silver fluoride and the commercially available chiral base dihydrocinchonine **61** (Scheme 17) proceeded with high *endo*-diastereoselectivity and moderate enantioselectivity (up to



Scheme 18 Enantioselective 1,3-DCR of azomethine ylide precursors **3** with acrylates mediated by chiral base **61**

73% ee and up to 92% ee after recrystallization). It is worth noting that the use of less stable aliphatic imino esters **3** (R^1 = Cy, *i*Pr, and *t*BuCH_2) gave good yields when it is very well known [29] that these substrates afford very large amounts of products derived from the Michael-type addition reaction and poor yields of the expected cycloadducts. The *endo*-diastereoselectivity was excellent in all of the examples essayed (>98 : 2 *endo*:*exo* ratio), however, the enantioselectivity of these processes was moderate (32–73% ee and one example with 92% ee after recrystallization). The amounts of base (with a quinuclidine nucleus) required was 5 mol %, and the presence of Ag cation was crucial in order to fix the dipole conformation. A compact ionic pair composed by the Ag-dipole and the chiral ammonium salt is the presumed key intermediate for the observed enantioselectivity.

The chiral PTC agent **63** (Fig. 7) in combination with CsOH as base, have been used for enantioselective additions of iminoglycinates or α-substituted iminoglycinates onto electrophiles for the synthesis of α-amino acids [16]. Although, initially the system was essayed for the Michael-type addition reaction, some effort also was directed to the enantioselective 1,3-DCR between **3** (R^1 = 2-HOC_6H_4, R^2 = Me) and methyl acrylate. Unfortunately, the enantioselectivity achieved for the corresponding *endo*-**13** (R^3 = H) was quite low (up to 25% ee) and the chemical yield moderate [58].

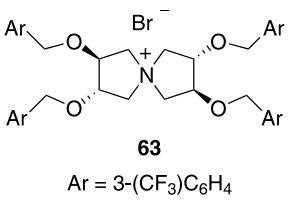


Fig. 7 Chiral PTC agent **63**

5 Final Remarks

The cycloaddition reactions described in this review are amazing examples of stereochemical selectivity. It is fantastic to be able to obtain one of the 16 possible stereoisomers in only one step using a minimal amount of catalyst, and even working with a catalyst able to control and generate the adduct with the opposite absolute configuration, simply by a small structural variation on the chiral ligand. All these efforts have been dedicated to a very complex reaction with many parameters to consider, especially the structure of the dipole and of the dipolarophile, and how to bring them closer to the central metal coordination sphere.

Chiral Ag(I)-complexes afforded exclusively the *endo*-cycloadducts. However, as has been described, chiral Cu(I)-complexes generated *endo*- and *exo*-cycloadducts, although the general preference of Cu(I) systems is to yield the *exo*-adducts. The Zn(II)-complexes are not as enantioselective as the Ag or Cu complexes and the chiral base induction in 1,3-DCR is still far away in achieving excellent ee of the proline derivatives. Finally, organocatalysts only afforded impressive results in a very restricted structural array of substrates and the main applications of this methodology are not as promising as those predicted for the metal catalyzed 1,3-DCR. Much work still has to be invested into these catalytic enantioselective 1,3-DCR reactions in order to improve the general selectivity in all type of dipoles and dipolarophiles, the recovery of catalyst and the employment of minimal amounts of reagents.

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Heterocycles by Cycloadditions of Carbonyl Ylides Generated from Diazo Ketones

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Abstract Carbonyl ylide dipoles are important intermediates with great application in heterocyclic chemistry. Here, we show how the rhodium-catalyzed α-diazocarbonyl compounds are employed in the generation of carbonyl ylides and their effective use for the synthesis, as well as functionalization, of heterocycles. Herein we discuss recent advancements in this field mainly describing the synthesis and importance of various oxygen- and nitrogen-containing heterocyclic systems and natural products from α-diazocarbonyl compounds.

Keywords 1,3-Dipolar cycloaddition · Carbonyl ylide · Diazocarbonyl compounds · Heterocyclic compounds · Rhodium(II) acetate

Abbreviations

Ac	Acetyl
BHA	Benzhydrylamine
t-Bu	*tert*-butyl
Cbz	Benzyloxycarbonyl
$Cu(acac)_2$	Copper(II) acetylacetonate
CuOTf	Copper(I) triflate
$Cu(OTf)_2$	Copper(II) triflate
dr	Diastereomeric ratio

DMAD	Dimethyl acetylenedicarboxylate
ee	Enantiomer excess
Et	Ethyl
Me	Methyl
MOM	Methoxymethyl
NPM	*N*-phenylmaleimide
Ph	Phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
i-Pr	Isopropyl
Pybox	2,6-bis(oxazolinyl)pyridine
$Rh_2(OAc)_4$	Dirhodium(II) acetate
$Rh_2(5R\text{-MEPY})_4$	Dirhodium(II) tetrakis[methyl 2-oxopyrrolidin-5-carboxylate]
$Rh_2(oct)_4$	Dirhodium(II) octanoate
$Rh_2(pfbm)_4$	Dirhodium(II) perfluorobutyramidate
$Rh_2(pfm)_4$	Dirhodium(II) perfluorobutyroamidate
$Rh_2(pfb)_4$	Dirhodium(II) perfluorobutyrate
$Rh_2(S\text{-BPTV})_4$	Dirhodium(II) tetrakis[*N*-benzene-fused-phthaloyl-(*S*)-valinate]
$Rh_2(R\text{-DDBNP})_4$	Dirhodium(II) tetrakis(1,1′-binaphthyl-2,2′-diylphosphate)
$Rh_2(S\text{-DOSP})_4$	Dirhodium(II) tetrakis[*N*-[(4-dodecylphenyl)sulfonyl]-(*S*)-prolinate]
$Rh_2(S\text{-PTTL})_4$	Dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate]
TBDPS	*Tert*-butyldiphenylsilyl
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
p-TSA	*p*-toluenesulfonic acid
$Yb(OTf)_3$	Ytterbium(III) triflate

1 Introduction

The metal-catalyzed decomposition of diazo compounds in the presence of carbonyl compounds is a well-established reaction to generate a carbonyl ylide intermediate. Several new developments have revolutionized this area of chemistry and are included in this review. Most notably, major advances have occurred in catalyst design, such that highly chemoselective, diastereoselective and enantioselective carbenoid transformations can now be achieved. Furthermore, it has been recognized that a wide array of carbenoid structures can be utilized in this chemistry, leading to a broad range of synthetic applications.

Herein rhodium-catalyzed inter- and intramolecular cycloadditions of carbonyl ylides derived from a range of diazocarbonyl compounds leading to oxygen- and nitrogen-containing heterocyclic systems and natural products are discussed. We have focussed on the last five years for the most significant developments of the reactions of carbonyl ylides derived from diazocarbonyl compounds.

Metal-carbenoid intermediates derived from diazo compounds undergo a variety of useful reactions, including ylide formation, cyclopropanation and insertion. In recent years, several excellent reviews [1–19] and books [20–29] have appeared on various aspects of this chemistry. Several reviews on carbenoid chemistry have major sections on 1,3-dipolar cycloadditions of carbonyl ylides. Because of the historical central prominence of carbenoids derived from diazocarbonyl compounds, most reviews have tended to focus on these species. These carbenoids are capable of generating carbonyl ylide dipoles via inter- or intramolecular reactions (Fig. 1).

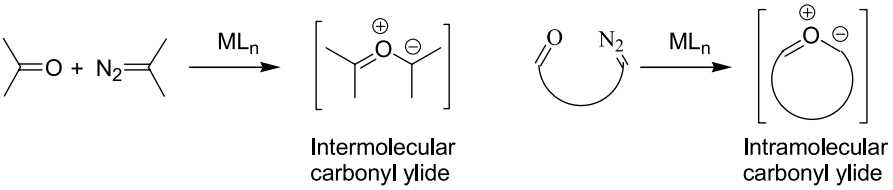


Fig. 1 Formation of carbonyl ylides

Herein, a comparison is presented of the chemical differences that exist among the 1,3-dipolar cycloaddition reactions of acyclic or cyclic carbonyl ylides with the major classes of dipolarophiles. It is hoped that this work will provide a useful reference and stimulate further efforts in this sphere, which has further potential for varied synthetic applications towards heterocycles and natural products.

The cycloaddition reaction of dipoles has been known since the 18th century, later, Huisgen introduced the concept of a 1,3-dipole [30]. One of the earliest examples of copper(II) acetylacetonate [$Cu(acac)_2$] catalyzed 1,3-dipole formation involved the controlled decomposition of an α-diazo ketone [31]. Some cases utilized copper as the metal species and demonstrated the feasibility of cycloaddition reactions and these 1,3-dipoles with dipolarophiles. These reactions set the stage for the evaluation of additional transition metals capable of catalyzing this transformation. The earliest example of rhodium(II)-catalyzed α-diazo ketone decomposition to form a 1,3-dipole was described by Teyssie and co-workers [32]. Despite this promising beginning, it was not until many years later that rhodium(II) was used generally for the formation of such 1,3-dipoles [6–12, 21, 29, 30] (Fig. 1).

Carbonyl ylides were proposed as intermediates in 1965 during the cycloaddition reaction of substituted epoxides [33]. Many strategies are known in the literature to generate the transient carbonyl ylides. Among these methods are thermolysis or photolysis of epoxides having electron-withdrawing substituents [34–38], the thermal extrusion of nitrogen from 1,3,4-oxadiazolines [39–43], extrusion of carbon dioxide from 1,3-dioxolan-4-ones [44, 45], addition of organometallic reagents [46], mesoionic carbonyl

ylides from the corresponding pyranulose acetates with base [47] and the photolysis of diazo compounds in noble gas matrixes [48]. The easiest route to the transient carbonyl ylides is through the addition of a metallocarbenoid derived from a diazo precursor onto the oxygen atom of a carbonyl group. The transition metal catalytic route to carbonyl ylides from diazocarbonyl compounds is a facile process that can be either intermolecular or intramolecular. Intramolecular carbonyl ylide formation and their reactions have been more extensively studied in contrast to intermolecular carbonyl ylides as it appears that very limited examples are available of the intermolecular carbonyl ylide formation and their reactions [1–13, 49–53].

The reaction of α-diazocarbonyl compounds with transition metals provides stabilized carbenoids. The metallocarbenoids formed by this method are highly electrophilic on carbon and readily add nucleophiles, such as the oxygen end of many carbonyl derivatives, to form carbonyl ylides. Carbonyl ylides are highly reactive dipoles and readily participate in 1,3-dipolar cycloaddition (Scheme 1). The search of practical methods for generating carbonyl ylides has resulted in a plethora of activity directed towards the acquisition of complex heterocyclic frameworks and diverse natural products. Initially, the generation and trapping of a cyclic six-membered ring carbonyl ylide were demonstrated by Ibata and co-workers [54] and this has culminated in the development of a very versatile methodology for the construction of complex and highly functionalized heterocyclic compounds.

Despite the great synthetic utility of diazocarbonyl compounds in the generation of carbonyl ylide intermediates, definitive mechanistic studies on the metal-catalyzed cycloaddition of carbonyl ylides are scarce. Among the various metal catalysts, dirhodium(II) catalysts are the most effective and versatile for diazo decomposition. Because of the rapid catalytic turnovers of these reactions, structural information about the intermediates is difficult to obtain. A reasonable mechanism can be rationalized on the basis of product distribution, and especially on the basis of enantioselective outcome of various carbonyl ylide reactions [55–63].

Recently, some significant advances have been made that will likely have a major impact on the mechanistic understanding of these transformations. A stable rhodium-carbenoid complex has been characterized by X-ray crystallography [64]. As these systems are also capable of inducing catalytic carbenoid transformations, the X-ray crystallographic data lead to definitive information about the key metal carbenoid intermediate in catalytic reactions.

It is generally accepted that a typical carbonyl ylide reaction proceeds as shown in Fig. 2. Interaction of diazo compound **1** with the metal forms diazonium complex **2**, which then extrudes nitrogen forming carbenoid intermediate **3**. Reaction of **3** with the carbonyl group present in the substrate forms intramolecular carbonyl ylide **4** (or an intermolecular carbonyl ylide) in which the metal catalyst may or may not remain associated with the ylide [13]. Finally, the [3+2]-cycloaddition and regeneration of the active cat-

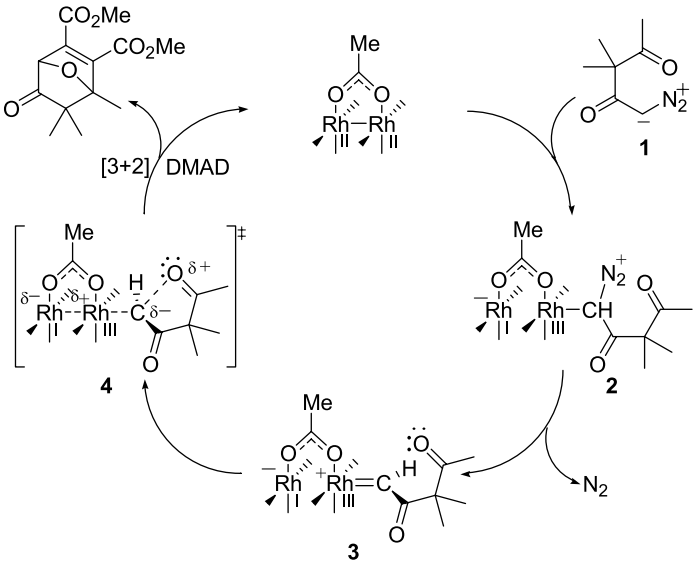


Fig. 2 General mechanism

alyst occur simultaneously. For most catalysts, attack of the carbonyl oxygen on the carbenoid is generally considered to occur without coordination of the oxygen to metal.

Herein we deal with cycloaddition reactions of inter- as well as intramolecular carbonyl ylides towards the construction of functionalized five-membered heterocycles and oxa-bridged carbocyclic and heterocyclic sys-

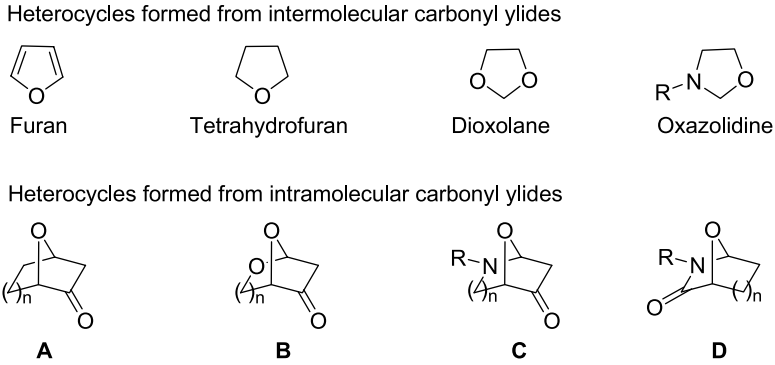
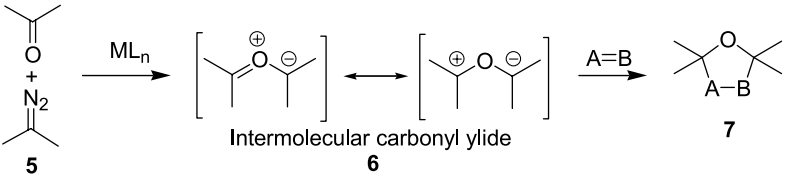


Fig. 3 **A** Oxabicyclo[2.2.1]heptan-2-one ($n = 1$); oxabicyclo[3.2.1]octan-2-one ($n = 2$); oxabicyclo[4.2.1]nonan-2-ones ($n = 3$). **B** Dioxabicyclo[2.2.1]heptan-5-one ($n = 1$); dioxabicyclo[3.2.1]octan-2-one ($n = 2$). **C** Oxazabicyclo[2.2.1]heptan-5-one ($n = 1$); oxazabicyclo[3.2.1]octan-2-one ($n = 2$). **D** Oxazabicyclo[2.2.1]heptan-3-one

tems, respectively (Fig. 3). In fact, these heterocyclic ring systems can be easily assembled from α-diazocarbonyl compounds.

2
Rhodium-Catalyzed Intermolecularly Generated Carbonyl Ylides

The synthesis of highly substituted furan, tetrahydrofuran, dioxolane and oxazolidine systems that are found in many biologically interesting natural products, has attracted considerable attention in recent years. These heterocyclic ring systems have conveniently been assembled via intermolecularly generated carbonyl ylide 1,3-dipoles. The transient intermolecular carbonyl ylides are usually generated by addition of a metallo-carbenoid derived from a diazo precursor onto the oxygen atom of a carbonyl group (**5**) (Scheme 1). These transient carbonyl ylides **6** generated by a catalytic route can be readily trapped inter- or intramolecularly with π-bonds in a 1,3-dipolar cycloaddition reaction to afford oxygen heterocycles **7**.

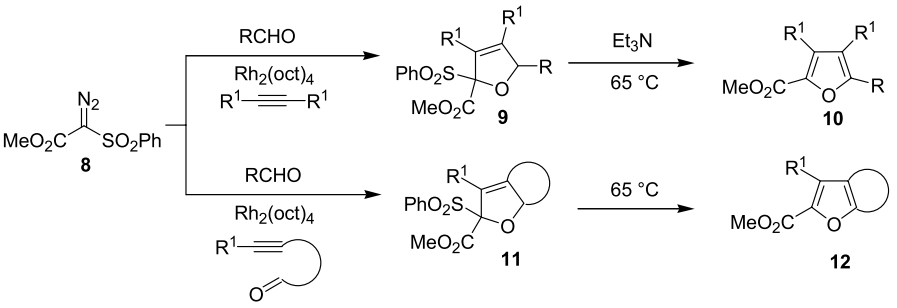


Scheme 1

2.1
Synthesis of Furan, Tetrahydrofuran, Dioxolane and Oxazolidine Ring Systems

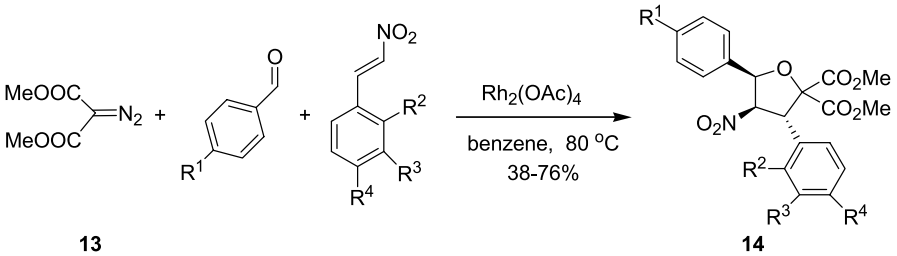
Synthesis of furans has been carried out via three-component reactions involving intermolecular carbonyl ylide formation. Johnson and co-workers have revealed [65] the consequence of intermolecular carbonyl ylide generation followed by trapping with a selective dipolarophile to obtain furan ring systems. On the basis of this approach, the diazosulfone **8** underwent intermolecular reaction with aldehydes in the presence of $Rh_2(oct)_4$ to form carbonyl ylide intermediates, which could be trapped by alkynes in an inter- or intramolecular manner to yield substituted dihydrofurans **9** or **11**, which were later converted to furans **10** and **12**, respectively (Scheme 2).

The three-component reaction approach was also utilized to synthesize tetrahydrofurans. Reaction of dimethyl diazomalonate **13**, aryl aldehydes and β-nitrostyrenes afforded [66] tetrahydrofurans **14** in a highly stereoselec-



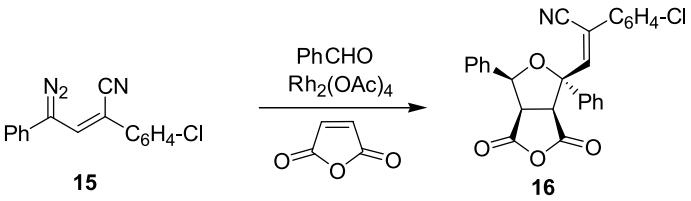
Scheme 2

tive manner. The stereochemistry of tetrahydrofuran **14** was attributed by the concerted nature of intermolecular carbonyl ylide formation followed by intermolecular 1,3-dipolar cycloaddition (Scheme 3).



Scheme 3

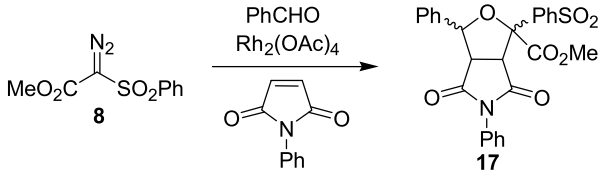
The vinyl carbonyl ylides from dirhodium(II) tetraacetate-catalyzed decomposition of the vinyldiazo compound **15** in the presence of aldehydes allowed the reaction with maleic anhydride to afford the stereoselective tetrahydrofurofuran ring systems **16** (Scheme 4) [67].



Scheme 4

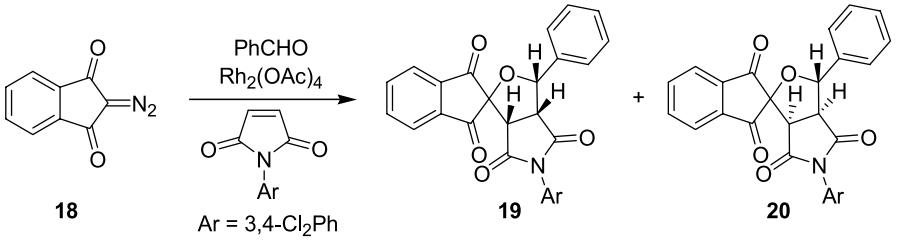
The synthesis of highly substituted furopyrroles, which are found in many biologically interesting natural products, has attracted considerable attention in recent years. Changing the dipolarophile from maleic anhydride to NPM

increased the efficiency of trapping the ylide that furnished the furopyrrole system **17** (Scheme 5) in good yield [67].



Scheme 5

A three-component reaction of 2-diazoindan-1,3-dione (**18**), benzaldehyde and substituted *N*-phenylmaleimide gave in good yield a mixture of spirofuropyrroles **19** and **20** possessing three stereocenters in good yields (Scheme 6). These compounds **19** and **20** were reported to be potent tRNA synthetase inhibitors with IC_{50} of 0.6 and 0.004 M, respectively [68].

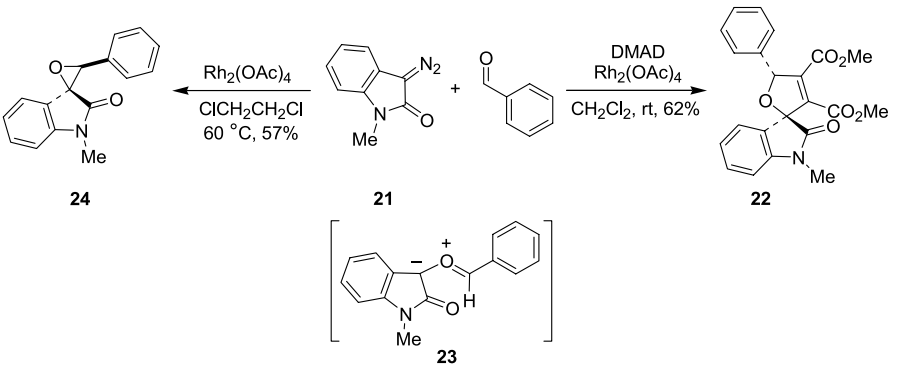


Scheme 6

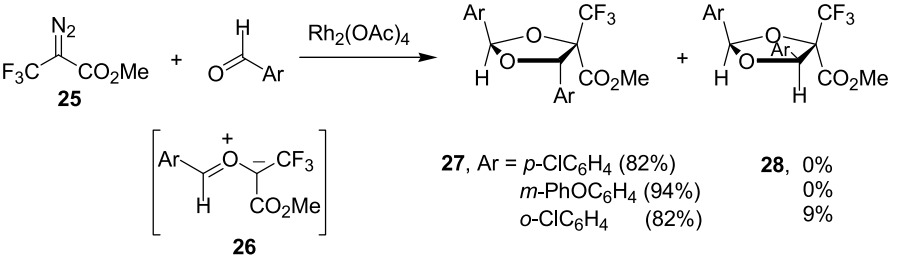
The diastereoselective synthesis of spirofurooxindoles has been described based on the three-component reaction involving intermolecular carbonyl ylide dipole **23** [69]. The reaction of 3-diazoindol-2-one **21**, benzaldehyde and DMAD in the presence of 0.5 mol % of rhodium(II) acetate catalyst furnished the spirofurooxindole **22** (Scheme 7). On the basis of the diastereoselectivity of these reactions, the conformation of the intermolecular carbonyl ylide **23** is provided. In the absence of dipolarophiles, the carbonyl ylide underwent electrocyclization to yield oxiranes **24** [70].

The synthesis of biologically important trifluoromethyl-substituted dioxolanes has been accomplished via 1,3-dipolar cycloaddition reaction of an intermolecularly generated carbonyl ylide with an aryl aldehyde. For example, the reaction of methyl diazo(trifluoromethyl)acetate (**25**) with two equivalents of aryl aldehydes afforded dioxolanes **27, 28** [71]. The diastereoselectivity of these reactions depends on the substituent present on the aryl aldehyde (Scheme 8).

The dioxolane ring system was also obtained via three-component reactions involving a diazo ester and electron-rich as well as electron-deficient

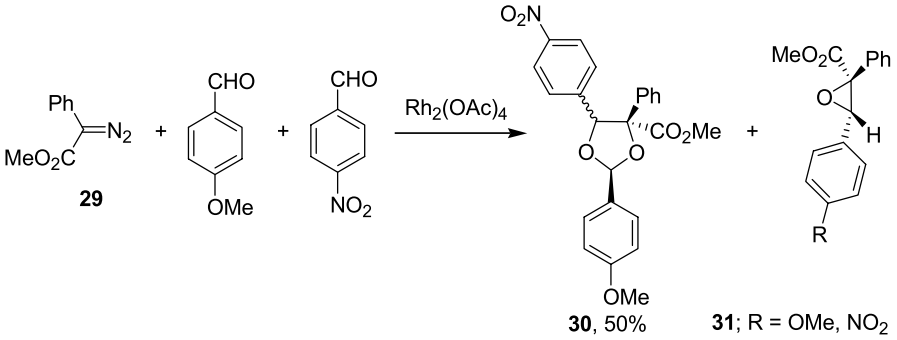


Scheme 7



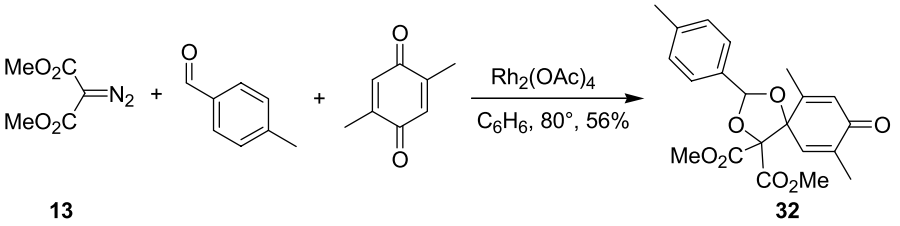
Scheme 8

aryl aldehydes. The electron-rich aryl aldehydes aid in generating the intermolecular carbonyl ylides and subsequent cycloaddition takes place with electron-deficient aryl aldehydes [72]. For example, the rhodium(II) acetate-catalyzed reaction of methyl phenyldiazoacetate **29**, *p*-anisaldehyde and *p*-nitrobenzaldehyde afforded dioxolanes **30** in moderate yields with minor amounts of epoxides **31** (Scheme 9). The divergence between the reactions of electrocyclization to oxiranes or 1,3-dipolar cycloaddition to dioxolanes has been also studied [73].



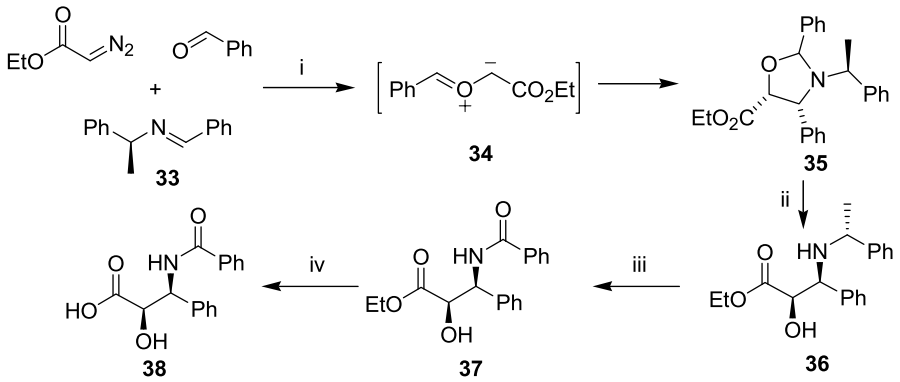
Scheme 9

The spirodioxolane **32** was synthesized in moderate to good yield [74] from a similar three-component reaction involving diazo ester, aryl aldehyde and *p*-benzoquinone. Here, *p*-benzoquinone acts as the dipolarophile to trap the intermolecular carbonyl ylide generated from **13** and the aldehyde (Scheme 10).



Scheme 10

An efficient protocol for the diastereoselective synthesis of oxazolidine **35** has been established based on the three-component reaction involving imine **33**, benzaldehyde and ethyl diazoacetate [75, 76]. The oxazolidine **35** obtained by this methodology was applied to a short enantioselective synthesis of the C-13 side chain of taxol **38** (Scheme 11).

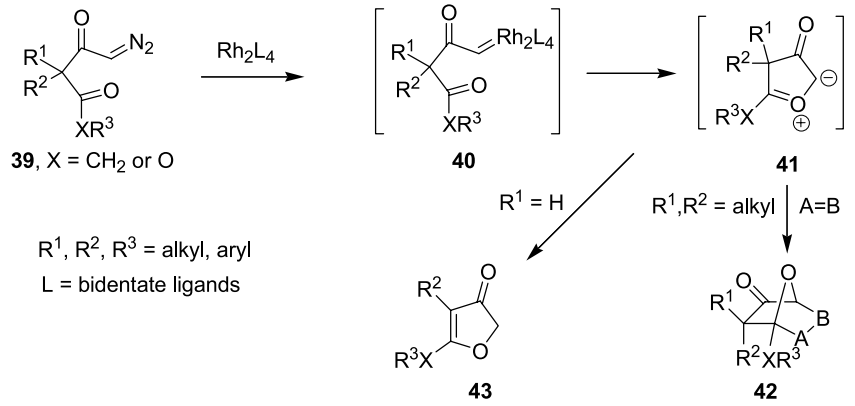


Scheme 11 Reagents and conditions: (i) $Rh_2(OAc)_4$ (2 mol %), 4-Å molecular sieves, CH_2Cl_2, 0 °C; (ii) *p*-TSA, MeOH/H_2O (95 : 5), rt (77%, 2 steps, d.r. 8 : 1 : 1); (iii-a) H_2, $Pd(OH)_2$, EtOH, 3 M HCl, rt; (iii-b) PhCOCl, $NaHCO_3$, EtOAc, 0 °C (77% over 2 steps); (iv) LiOH·H_2O, THF/MeOH/H_2O (10 : 5 : 4), rt (89%)

3
Rhodium-Catalyzed Intramolecularly Generated Carbonyl Ylides

When a diazo functionality positioned at the γ-position to a carbonyl group of a substrate is exposed to an appropriate transition metal catalyst, an

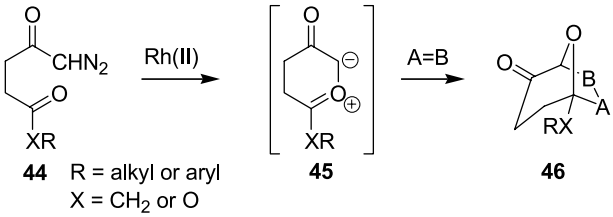
intramolecular five-membered ring carbonyl ylide dipole is formed as a transient species through transannular cyclization onto the neighboring keto carbonyl oxygen. The formation of less strained five-membered ring ylides is generally favored compared to other ring sizes [77]. The successful trapping of such five-membered ring carbonyl ylides depends on the substrate structure and the absence of competition from alternative intramolecular reaction pathways. As an example, the rhodium(II)-catalyzed reaction of substituted α-diazo ketones **39** generates initially the rhodium carbenoids **40**, followed by formation of the five-membered ring carbonyl ylides **41**, which can be trapped regio- and stereoselectively using a dipolarophile A=B to form the oxabicyclo[2.2.1]heptan-2-ones **42**. If R^1 is a hydrogen atom (see Scheme 12), the corresponding hydrogen migrated product **43** is observed; in this case the intramolecular proton transfer is faster than intermolecular 1,3-dipolar cycloaddition. From a synthetic perspective and to gain efficient access to the cycloaddition products **42**, it is important that competitive reactions like proton transfer and C-H insertion are avoided through a proper choice of the substrate **39**.



Scheme 12

When a substrate with a diazo functionality at the δ-position to the carbonyl group, e.g. **44**, is reacted with an appropriate transition metal catalyst, a cyclic six-membered ring carbonyl ylide **45** is formed as a transient species via transannular cyclization onto the δ-positioned carbonyl oxygen. These transient species **45** readily engage in inter- or intramolecular [3+2]-cycloadditions with a variety of dipolarophiles to furnish oxabicyclo[3.2.1]-octan-2-ones **46** (Scheme 13).

In general, both five- and six-membered ring carbonyl ylide intermediates in the presence of a transition metal catalyst are generated from a variety of carbonyl-bearing precursors such as ketones and esters. The cycloaddition



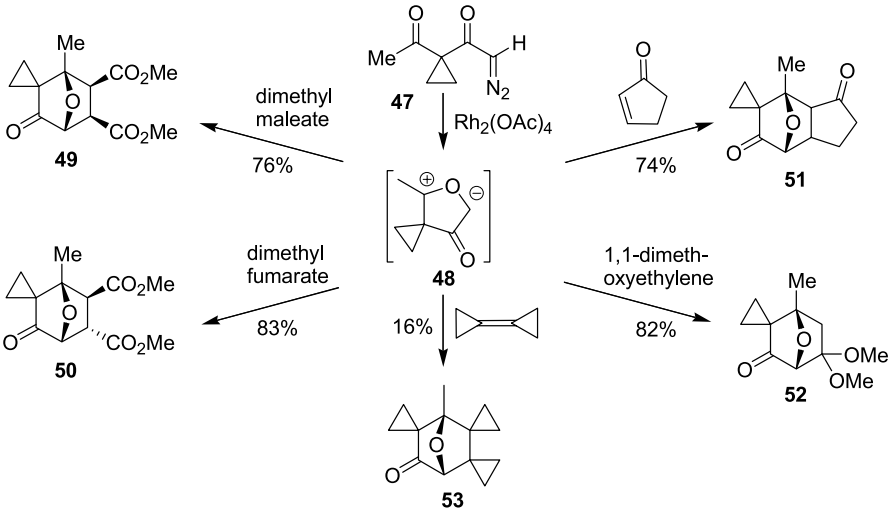
Scheme 13

reactions of carbonyl ylides derived from these carbonyl precursors towards various heterocyclic systems are discussed below.

3.1
Synthesis of Oxabicyclo[2.2.1]heptan-2-ones and Oxabicyclo[3.2.1]octan-2-ones

Oxabicyclo[2.2.1]heptan-2-ones

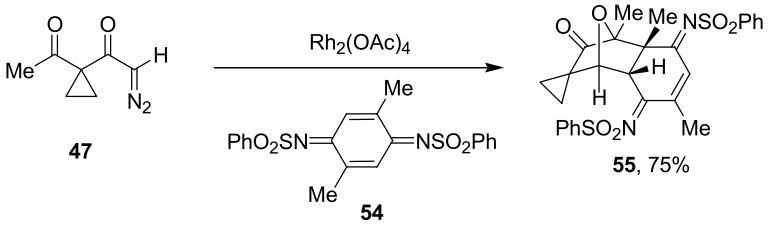
On the basis of the 1,3-dipolar cycloaddition of 5-membered ring carbonyl ylides, syntheses of oxabicyclo[2.2.1]heptan-2-one ring systems were successfully accomplished. For example, the reactions of the cyclopropyl-substituted five-membered ring carbonyl ylide **48** derived from the α-diazo ketone **47** with different dipolarophiles have been investigated [78–80]. The compound **47** undergoes cycloaddition in the presence of $Rh_2(OAc)_4$ with dimethyl maleate, dimethyl fumarate, cyclopentenone, 1,1-dimethoxyethylene and bicyclopropylidene furnishing the expected cycloadducts **49–53**, respectively



Scheme 14

(Scheme 14). The regiochemical outcome of the 1,3-dipolar cycloaddition reactions of the cyclic five-membered ring carbonyl ylide **48** with a variety of acyclic and cyclic alkenes having activated or inactivated π-bonds can be rationalized [78, 79] on the basis of frontier molecular orbital considerations, with the HOMO and LUMO of the carbonyl ylides dominating the reactions with electron-deficient and electron-rich dipolarophiles, respectively (Scheme 14).

The reactivity of the spirocyclic ylide **48** with *p*-quinoneimides such as **54** has also been probed and has been found to furnish the *endo*-adduct **55** (Scheme 15) in a chemo- and stereoselective manner [81].

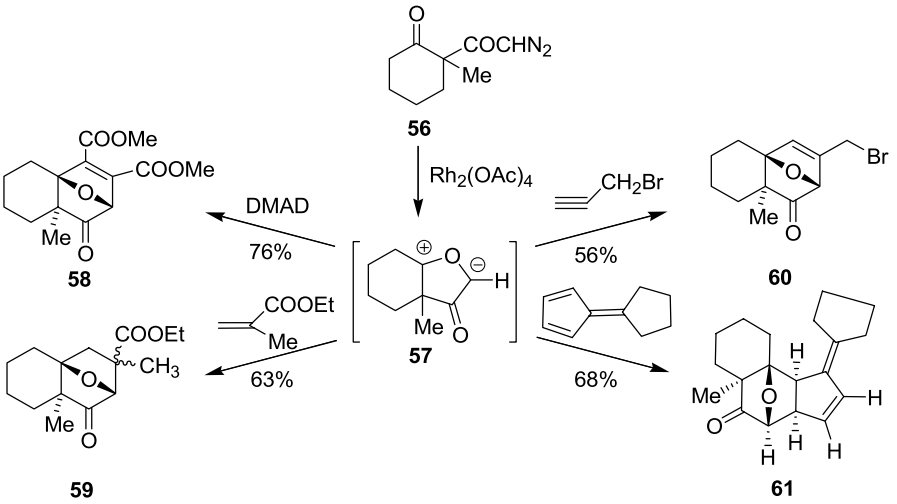


Scheme 15

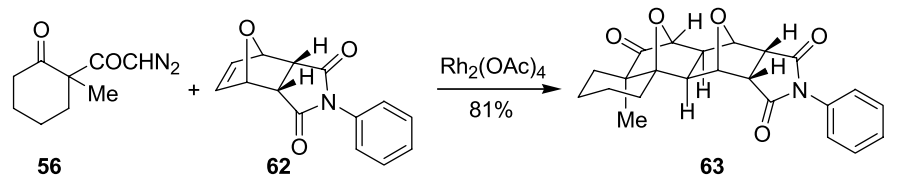
Muthusamy and co-workers have demonstrated [82] the reactions of the bicyclic ylide **57**, generated from the diazocarbonyl compound **56**, with symmetrical and unsymmetrical dipolarophiles. Thus, exposure of the cyclohexanone-substituted α-diazocarbonyl compound **56** to DMAD in the presence of $Rh_2(OAc)_4$ as the catalyst has furnished the cycloadduct **58** (Scheme 16). This cycloaddition was diastereoselective and, in the case of unsymmetrical dipolarophiles such as methyl methacrylate and propargyl bromide, they were regioselective and afforded oxygen heterocycles **59** and **60**, respectively. The same research group has reported the 1,3-dipolar cycloaddition of the bicyclic carbonyl ylide **57** with other dipolarophiles, namely fulvenes [83]. In these tandem cyclization–cycloaddition reactions involving fulvenes, four stereocenters and two new C–C bonds are formed in a single step. Symmetrical dipolarophiles such as macrocyclic olefins were also used for diastereoselective 1,3-dipolar cycloaddition reaction with **56** [84].

An efficient protocol for the synthesis of *syn*-facially bridged norbornane frameworks has been developed via the tandem cyclization–cycloaddition reactions of the carbonyl ylide **57** with norbornene derivatives. The reaction of the diazo ketone **56** with the dipolarophile **62** in the presence of $Rh_2(OAc)_4$ furnished [85] the *syn*-facially bridged oxa-norbornane framework **63** in high yield (Scheme 17).

The 1,3-dipolar cycloaddition of the diazocarbonyl compound **56** with heterocyclic compounds, namely indoles, has been studied by Muthusamy and co-workers [86, 87]. Intermolecular cycloaddition of the fused five-membered

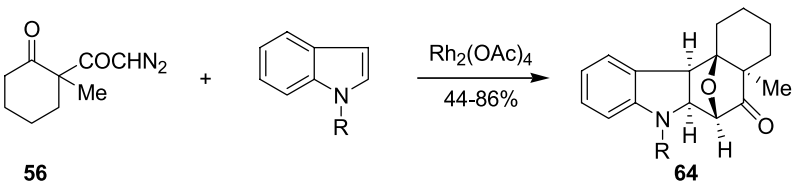


Scheme 16



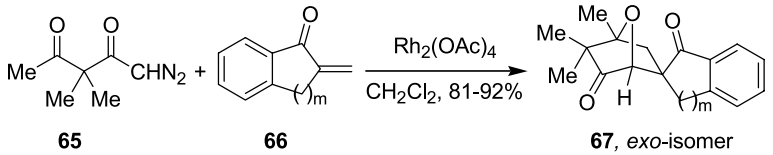
Scheme 17

ring cyclic carbonyl ylide **57**, derived from **56**, with indole, *N*-methylindole and *N*-benzylindole afforded the decahydrobenzo[*c*]carbazole skeleton **64** with high regioselectivity (Scheme 18). With an electron-withdrawing group on the indole nitrogen, however, regioisomeric decahydrobenzo[*a*]carbazoles are also obtained.



Scheme 18

An efficient approach to synthesize spiroheterocycles **67** (Scheme 19) with various ring sizes via rhodium(II)-catalyzed tandem cyclization-1,3-dipolar cycloaddition reaction was developed that features a rapid construction of

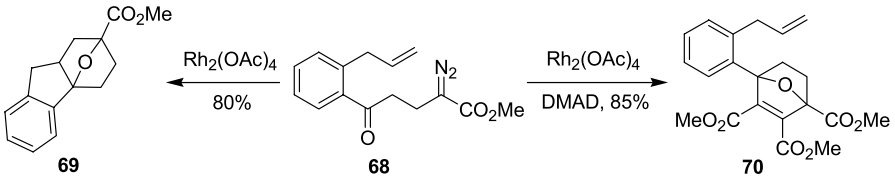


65 66 67, *exo*-isomer

Scheme 19

the oxa-bridged spiro compounds under mild conditions with high regio-, chemo- and diastereoselectivities [88].

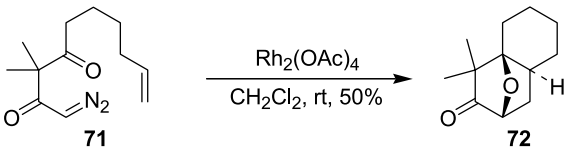
An intramolecular variant of the five-membered ring carbonyl ylide cycloaddition has also been explored [89]. When the specially crafted α-diazo ketoester **68** was decomposed in the presence of $Rh_2(OAc)_4$, an intramolecular cycloaddition product **69** was realized in good yield (Scheme 20). On the other hand, if DMAD was present in the reaction mixture, the bimolecular adduct **70** was isolated.



69 68 70

Scheme 20

The formation of 5-membered ring carbonyl ylides from a δ-keto functionality was shown to undergo the intramolecular [3+2]-cycloaddition with alkenes or alkynes. An illustrative example [79] is the reaction of acyclic diazo ketone **71** with a catalytic quantity of rhodium(II) acetate at room temperature to afford the polycyclic adduct **72** in 50% yield with complete diastereoselectivity (Scheme 21). This example shows that the intramolecular cycloadditions of 5-membered ring carbonyl ylide can take place across the unactivated 1-hexenyl π-bond.

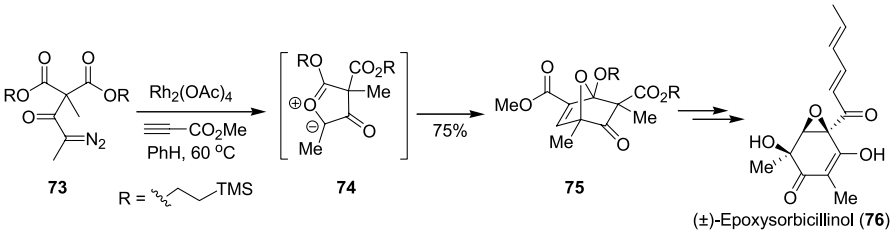


71 72

Scheme 21

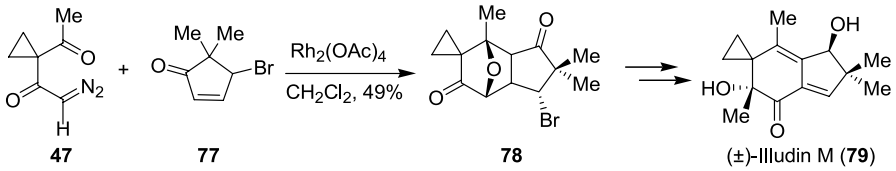
The utility of an ester-derived five-membered ring carbonyl ylide dipole has been demonstrated in the first total synthesis of the biologically active natural product, (±)-epoxysorbicillinol (**76**) [90], a novel vertinoid polyketide possessing an epoxide functionality. The rhodium(II)-catalyzed decom-

position of the α-diazo ketone **73** in the presence of methyl propiolate furnished the diastereomerically pure oxabicycle **75** via the intermediate ylide **74** in good yield (Scheme 22). After functional group transformations, a synthesis of the natural product, (±)-epoxysorbicillinol (**76**), was accomplished.



Scheme 22

In another important application of this methodology, (±)-illudin M (**79**), a toxic sesquiterpene [91, 92] isolated from the jack-o'-lantern mushroom, has been synthesized [93] by Kinder and co-workers via the spirocyclic carbonyl ylide **48**. $Rh_2(OAc)_4$-mediated decomposition of α-diazo ketone **47** in the presence of cyclopentenone **77** afforded the key cycloadduct **78** as a single diastereomer, bearing the complete skeleton of the natural product. Functional group manipulations of the adduct **78** led to a total synthesis of (±)-illudin M (**79**) (Scheme 23). Padwa and co-workers also executed the syntheses of illudin, ptaquilosin and the closely related isodehydroilludin [78, 94] using carbonyl ylides. This carbonyl ylide cyclization–cycloaddition cascade approach (Scheme 23) has been further extended towards a short synthesis of the acylfulvenes [95], pterosin [79] and pterosin family of sesquiterpenes [96–99].

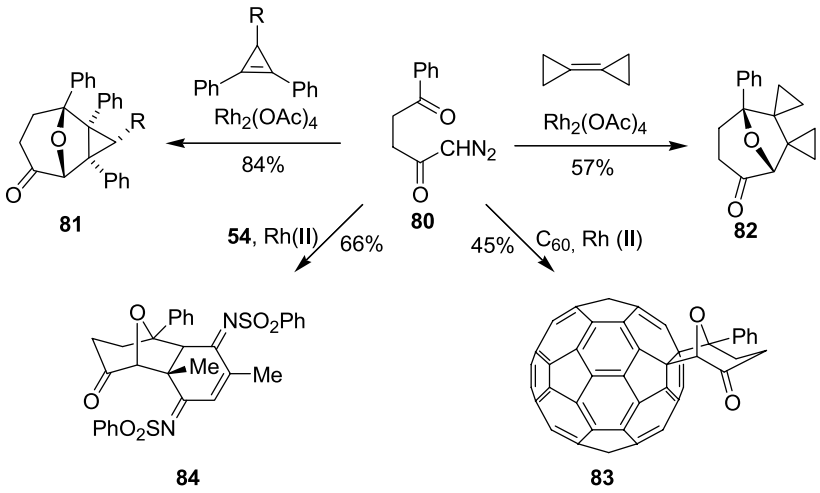


Scheme 23

Oxabicyclo[3.2.1]octan-2-ones

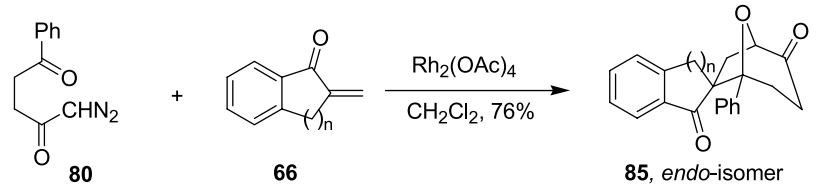
The synthesis of the oxabicyclo[3.2.1]octan-2-one ring system was successfully accomplished via the 1,3-dipolar cycloaddition of 6-membered ring carbonyl ylides. In a reactivity profile similar to that of the five-membered carbonyl ylides (see Schemes 14, 15), the carbonyl ylide derived from 1-diazo-

5-phenylpentane-2,5-dione (**80**) was shown to cycloadd to 1,2-diphenylcyclopropenes and bicyclopropylidene to give respective highly strained cyclopropanated oxa-bridged heterocyclic systems **81** and **82** in good yields with high stereoselectivity. Further studies of the stereochemical factors involved in the cycloaddition of carbonyl ylides with methylenecyclopropanes were also accomplished [80, 100]. Novel C_{60} fullerene derivatives of the type **83** have been synthesized through 1,3-dipolar cycloaddition reactions of six-membered carbonyl ylides with [60]-fullerene [101]. Similarly, reaction of diazo ketone **80** with *p*-quinoneimide afforded [81] the oxa-bicyclic compound **84** in good yield (Scheme 24).



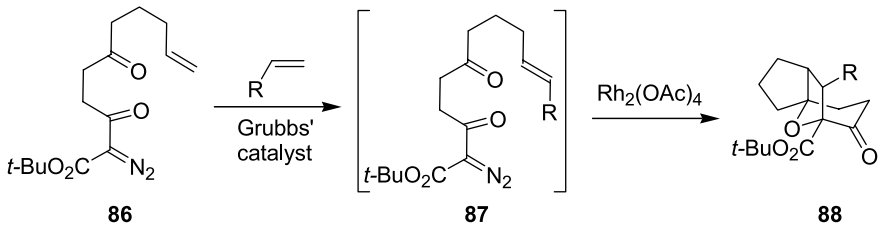
Scheme 24

Synthesis of *endo* spiro-oxabicyclo[3.2.1]octan-2-ones **85** has been reported based on the reaction of the six-membered ring carbonyl ylide generated from the diazo ketone **80** with α-methylene ketones (Scheme 25) [88]. Importantly, the reverse stereoselectivity was observed between the reactions involving five-membered ring carbonyl ylide intermediates and **66**, which led to *exo* spiro compounds (see Scheme 19).



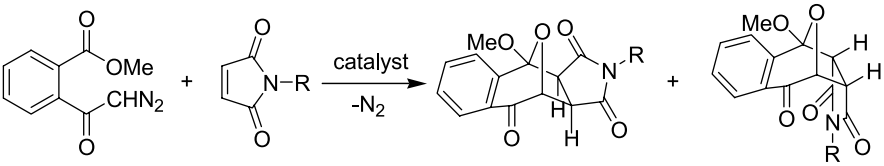
Scheme 25

Chemoselective alkene cross metathesis using Grubbs' catalyst, followed by $Rh_2(OAc)_4$ catalyzed tandem carbonyl ylide formation-intramolecular cycloaddition was demonstrated, thus establishing the compatibility of these two transition metal complexes sequentially catalyzing different carbene transfer reactions [102, 103]. Metathesis reaction of unsaturated diazo ester **86** with substituted olefins was studied using Grubbs' catalyst. With or without purification of the product, the disubstituted olefin **87** underwent cyclization–cycloaddition reaction catalyzed by $Rh_2(OAc)_4$ to afford oxa-bridged cycloadducts **88** (Scheme 26). Without purifying compound **87**, the reaction was conducted in a one-pot operation to furnish **88** in better yields.



Scheme 26

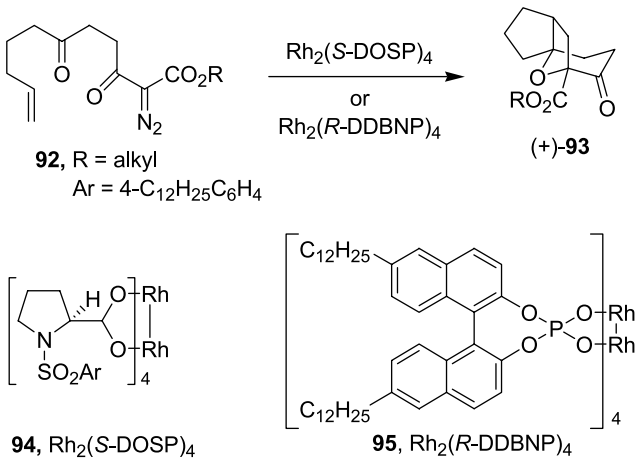
The first examples of dramatic changes in stereoselectivity caused by the metal catalysts and Lewis acids in 1,3-dipolar cycloadditions of carbonyl ylides derived from ester carbonyl compounds with *N*-substituted maleimides have been reported [104]. The decomposition of *o*-(methoxycarbonyl)-α-diazoacetophenone (**89**) in the presence of NPM using a range of typical metal catalysts (5 mol %) for the decomposition of the diazo compound afforded **90** and **91** as the *exo* and *endo* cycloadducts, respectively (Scheme 27). Surprisingly, when metal catalysts possessing Lewis acidity such as CuOTf (*endo/exo* = 87 : 13) and $Cu(OTf)_2$ (*endo/exo* = 82 : 18) were used, highly *endo*-selective 1,3-dipolar cycloaddition occurred which is not usually observed in carbonyl ylide cycloadditions. An even higher *endo* selectivity (*endo/exo* = 94 : 6) was observed by adding 5 mol % of $Yb(OTf)_3$ under 5 mol % of CuCl-catalyzed conditions. On the other hand, the reaction involving the use of $Rh_2(OAc)_4$ showed higher *exo* selectivity (*endo/exo* = 11 : 89).



Scheme 27

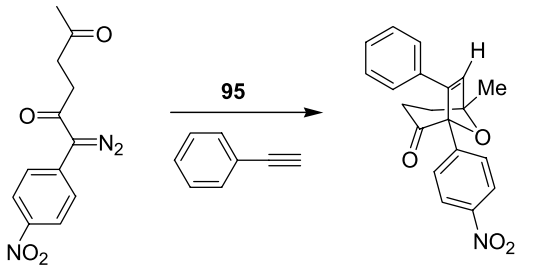
The results suggest that the Lewis acid controls the stereoselectivity in the 1,3-dipolar cycloaddition of carbonyl ylides by coordination to the dipolarophiles, as reported [105, 106] for the reactions of nitrones.

As an application to asymmetric synthesis for oxabicyclo[3.2.1]octan-2-ones ring systems, an enantioselective version of the tandem six-membered ring carbonyl ylide formation-intramolecular cycloaddition of α-diazocarbonyl compounds using chiral rhodium(II) carboxylates was successfully demonstrated for the first time by Hodgson and co-workers [107]. For example, the reaction of α-diazo-β-ketoesters **92** using 1 mol % of Rh_2(*S*-DOSP)$_4$ **94**, as catalyst gave [108] the oxa-bridged cycloadducts **93** via the six-membered carbonyl ylides with enantioselectivites of up to 53% ee (Scheme 28). No specific rotation was, however, observed when the reaction was repeated using other catalysts such as $Rh_2(OAc)_4$ and Rh_2(5*R*-MEPY)$_4$.



Scheme 28

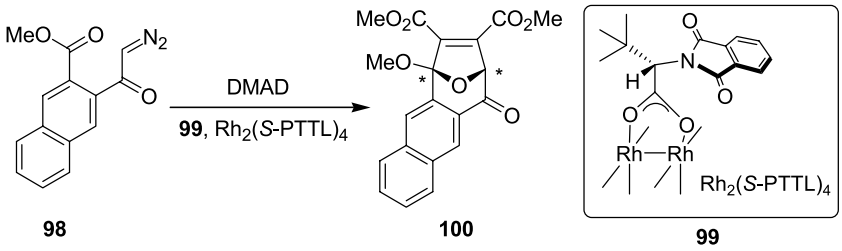
The same research group has also demonstrated a catalytic enantioselective tandem carbonyl ylide formation-cycloaddition of the α-diazo-β-ketoester **91** using 0.5 mol % of Rh_2(*R*-DDBNP)$_4$ **95**, as catalyst to afford the cycloadduct **93** in good yields (Scheme 28) with up to 90% ee [109]. A detailed study on enantioselective reaction using a series of dirhodium tetrakiscarboxylate and tetrakisbinaphtholphosphate catalysts under different solvent conditions has been described [56]. These studies indicate that dirhodium tetrakisbinaphtholphosphate catalysts are superior to the more commonly used carboxylates and carboxamidates in asymmetric transformations. Typically, the reaction [58] of the nitrophenyl-substituted diazodione **96** and phenyl acetylene in the presence of the binaphthyl catalyst **95** at 0 °C afforded the cycloadduct **97** with 76% ee (Scheme 29).



96 **97**; 83% (76% *ee*)

Scheme 29

Hashimoto and co-workers have shown the enantioselective 1,3-dipolar cycloaddition of the ester-derived carbonyl ylides using chiral dirhodium(II) carboxylates [110]. The ester-derived carbonyl ylide from the α-diazo ketone **98** in the presence (1 mol %) of Rh_2(*S*-PTTL)$_4$ **99** as the catalyst afforded the cycloadduct **100** with 93% ee (Scheme 30).

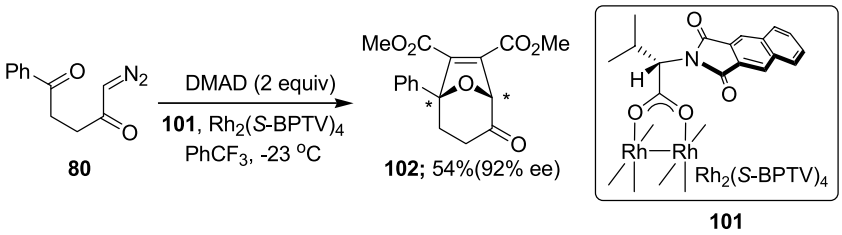


98 **100** **99**

Scheme 30

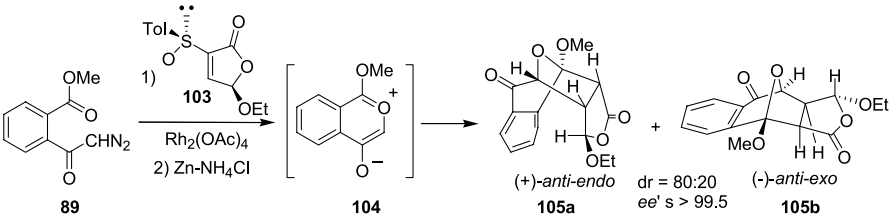
Another successful catalytic enantioselective 1,3-dipolar cycloaddition of α-diazocarbonyl compounds using phthaloyl-derived chiral rhodium(II) catalysts has been demonstrated [111]. Six-membered ring carbonyl ylide formation from the α-diazo ketone **80** and subsequent 1,3-cycloaddition with DMAD under the influence of 1 mol % of dirhodium(II) tetrakis[*N*-benzene-fused-phthaloyl-(*S*)-phenylvaline], Rh_2(*S*-BPTV)$_4$ **101** [112], has been explored to obtain the cycloadduct **102** in up to 92% ee (Scheme 31).

An important factor which could influence asymmetric induction would be that cycloaddition is faster than catalyst decomplexation from the ylide. Although the precise mechanism remains unclear, the high levels of enantioselection in intermolecular cycloadditions with dipolarophiles provide definite support for the intermediacy of a chiral rhodium(II)-associated carbonyl ylide involved in the cycloaddition step. These examples indicate that metal-catalyzed dipole formation followed by cycloaddition has the potential to be a powerful method for asymmetric synthesis.



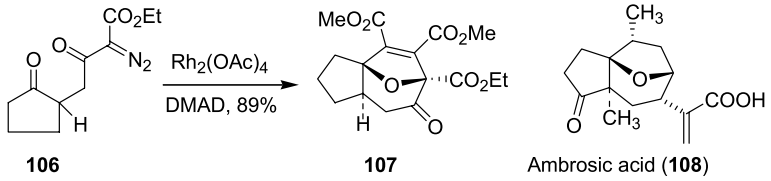
Scheme 31

The asymmetric induction on the 1,3-dipolar cycloaddition reaction of carbonyl ylides has also been studied using chiral dipolarophile. The $Rh_2(OAc)_4$-catalyzed reactions of *o*-(methoxycarbonyl)diazoacetophenone **89** with enantiomerically pure vinyl sulfoxides **103** afforded 4,10-epoxybenzo-[4,5]cyclohepta[1,2-*c*]furan-3,9-dione **105**, in good or moderate yield with complete regioselectivity [113]. The *endo* stereoisomer **105a** is favored with respect to the *exo* isomer **105b** and interestingly, high diastereoselectivity and complete enantioselectivity have been achieved (Scheme 32).



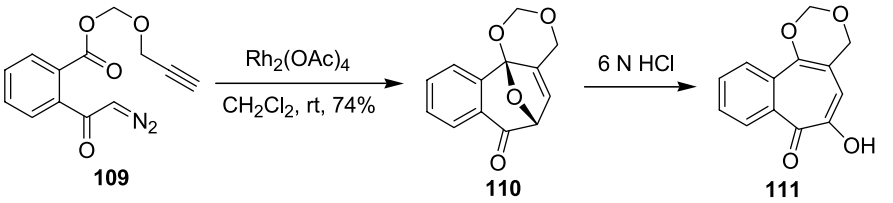
Scheme 32

The oxabicyclo[3.2.1]octan-2-one ring systems form a core skeleton of many naturally existing molecules. In an approach towards guaianolide sesquiterpenes, their hydroazulenic framework has been constructed through a rhodium(II)-catalyzed reaction [82] of the α-diazo ketone **106** with DMAD to afford the oxatricyclic system **107**, which forms the skeleton of ambrosic acid **108** (Scheme 33).



Scheme 33

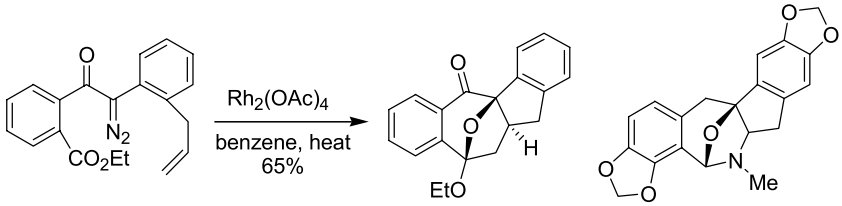
An intramolecular version of these reactions has also been reported. The generation of six-membered carbonyl ylides using ester carbonyl groups and their intramolecular trapping using acetylenic dipolarophile has been well documented in the synthesis of novel annulated benzotropolones [114] and was successfully applied to the synthesis of tropolone natural products. Exposure of the α-diazo ketone **109** to $Rh_2(OAc)_4$ resulted in the formation of a reactive metal-carbenoid intermediate which underwent intramolecular carbonyl ylide formation and subsequent 1,3-dipolar cycloaddition to give the tetracyclic compound **110** [115]. Acid-catalyzed ring opening in **110** yielded the tricyclic tropolone **111** with the methylene acetal still in place (Scheme 34).



109 **110** **111**

Scheme 34

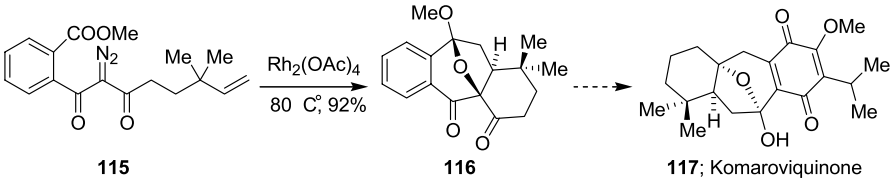
A series of α-diazo-β-(*o*-carbomethoxy)-substituted aryl ketones were prepared and employed as model systems for a synthetic approach towards the alkaloid, ribasine (**114**) [116]. The six-membered ring carbonyl ylide dipoles were generated from the *o*-allyl-substituted diazo ketoester **112** and $Rh_2(OAc)_4$ to access the cycloadduct **113** (Scheme 35). This result constitutes a promising model study towards the synthesis of the alkaloid, ribasine (**114**).



112 **113** Ribasine (**114**)

Scheme 35

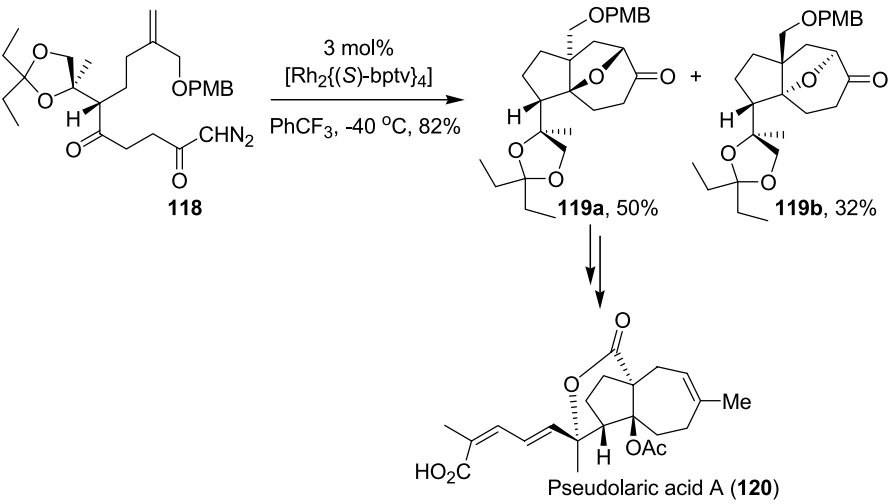
Natural quinones such as komaroviquinone **117** have been reported to show in vitro trypanocidal activity. An efficient approach to the core skeleton of komaroviquinone was accomplished by the Rh(II)-catalyzed reaction of the dimethyl-substituted diazo ester **115** to afford the oxatricyclo[6.3.1.$0^{0,0}$]dodecane skeleton **116** (Scheme 36) from an intramolecular [3+2]-cycloaddition



Scheme 36

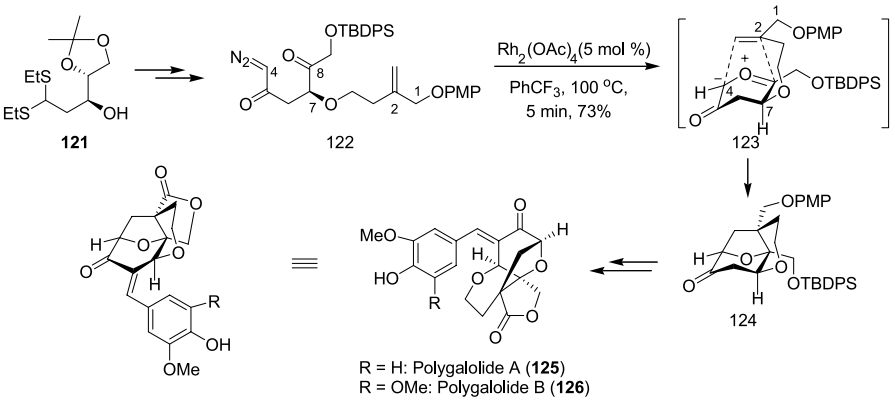
reaction of a carbonyl ylide dipole obtained by the interaction of a metallocarbenoid with an adjacent carbomethoxy group [117].

Intramolecular cyclization–cycloaddition cascade reactions of rhodium carbenoids have been deployed to devise an approach towards the cytotoxic diterpenoids, pseudolaric acids [118, 119]. Recently, pseudolaric acid A (**120**), possessing vast biological potential was successfully synthesized by Chiu and co-workers [120] (Scheme 37). The oxatricyclic intermediates **119a,b** were derived from an intramolecular cyclization–cycloaddition cascade process of acyclic diazoketone **118** in the presence of a chiral rhodium(II) catalyst. A series of further functional group manipulations of the desired major isomer **119a** has furnished pseudolaric acid A (**120**).



Scheme 37

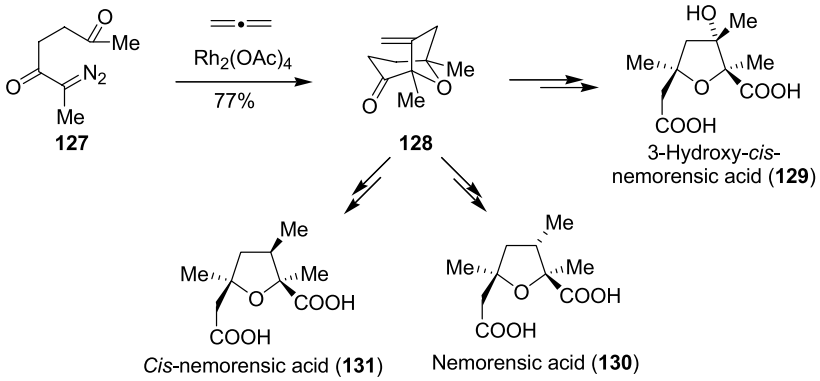
The enormous potential of this tandem carbonyl ylide formation-1,3-dipolar cycloaddition strategy has further been applied in the total synthesis of structurally complex polygalolides A and B (**125,126**). The synthesis illustrates the power of this methodology for rapid assembly of the unusual dioxatricyclic ring system **124** around the core oxabicyclo[3.2.1]octanone (Scheme 38). Thus, the first total synthesis of polygalolides A and B (**125,126**)



Scheme 38

was reported from alcohol **121**, with the longest linear sequence of 25 steps and with overall yields of 3.8% (**125**) and 3.2%, (**126**) respectively [121].

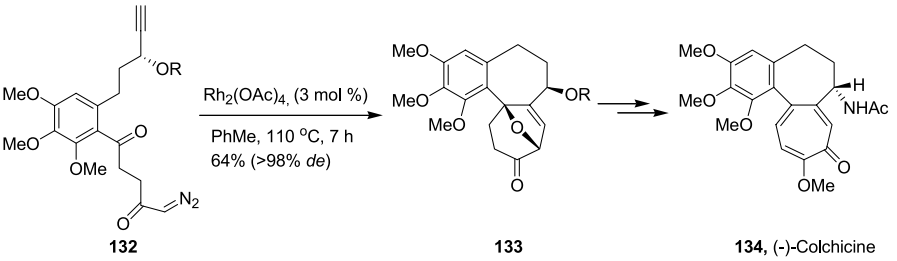
Concise and stereoselective syntheses of 3-hydroxy-*cis*-nemorensic acid (**129**), nemorensic acid (**130**) and *cis*-nemorensic acid (**131**) via a tandem carbonyl ylide-cycloaddition protocol have been demonstrated [57]. The successful use of allene as dipolarophile provided an opportunity to examine the reaction of such cumulenes with other stabilized carbonyl ylides, and the straightforward application of ester-directed hydrogenation to install the C-3 stereocenter in nemorensic acid. Oxa-bridged cycloadduct **128** was successfully subjected to further functional group modifications affording [122, 123] 3-hydroxy-*cis*-nemorensic acid (**129**), nemorensic acid (**130**) and *cis*-nemorensic acid (**131**) (Scheme 39).



Scheme 39

A synthesis of both of the antimitotic alkaloids (–)-colchicine (**134**) and its isomer (–)-isocolchicine was successively completed [124] using the synthetic

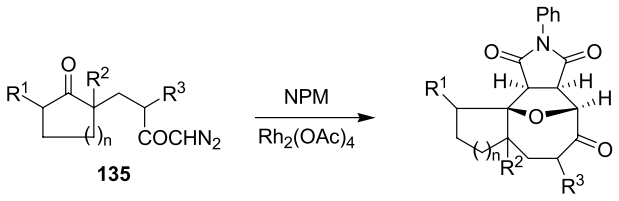
strategy of Rh-triggered cycloaddition cascade. In this case, the Rh-catalyzed transformation of α-diazoketone **132** into an oxatetracyclic key cycloadduct **133** through intramolecular [3+2]-cycloaddition of an in-situ generated carbonyl ylide was achieved. Further, the regioselective conversion of the cycloadduct **133** into a tropolone derivative led to an efficient enantioselective access to colchicine (Scheme 40).



132 **133** **134,** (-)-Colchicine

Scheme 40

Relatively little research effort has been reported with seven-membered ring carbonyl ylides which in turn will lead to oxabicyclo[4.2.1]nonan-2-ones [125]. In one example, the decomposition of compounds having a tethered diazocarbonyl functionality on the cycloalkanone ring systems **135** in the presence of $Rh_2(OAc)_4$ provided the seven-membered carbonyl ylides. This was demonstrated by trapping experiments using a dipolarophile like NPM to provide the cyclooctanoid systems **136** (Scheme 41).



135 **136**

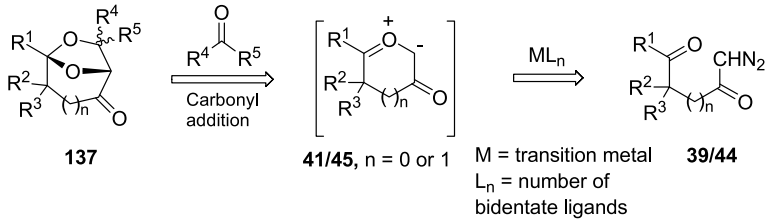
136a: n = 1; R^1, R^2 = H; R^3 = Me; 61%
136b: n = 2; R^1, R^2 = H; R^3 = Me; 58%
136c: n = 3; R^1, R^2,R^3 = H; 64%

Scheme 41

3.2 Synthesis of Dioxabicyclo[2.2.1]heptan-5-ones and Dioxabicyclo[3.2.1]octan-2-ones

The study of 1,3-dipolar cycloaddition reactions of cyclic carbonyl ylides with the C=O group has led to interesting results. In general, the reaction of a car-

bonyl ylide with a carbonyl group is expected to produce the dioxa-bridged bicyclic systems **137** via C=O cycloadditions as shown in Scheme 42.

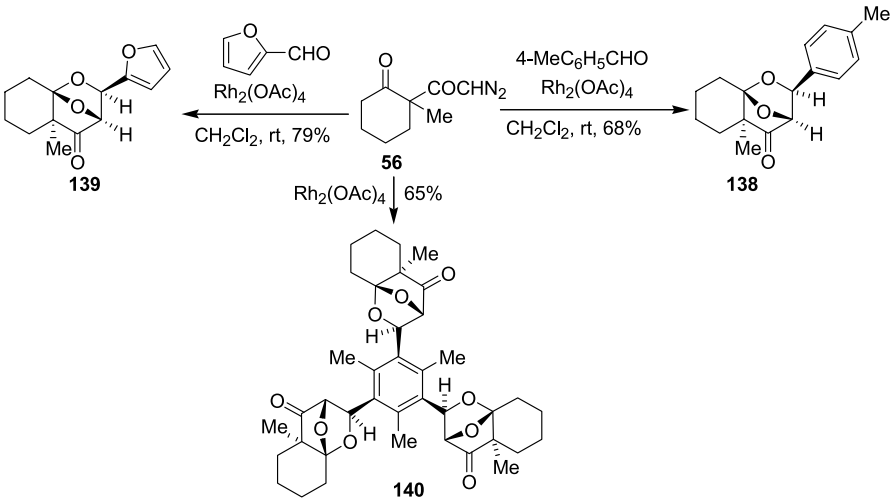


137 **41/45**, n = 0 or 1 **39/44**

Scheme 42

Dioxabicyclo[2.2.1]heptan-5-ones

Investigations and stereoselective studies on the tandem rhodium(II)-catalyzed reactions of α-diazocarbonyl compound **56** with various carbonyl compounds such as aromatic aldehyde and furan-2-carboxaldehyde have been studied by Muthusamy and co-workers [126] to provide the corresponding dioxatricyclic ring systems **138,139** with high regio- and chemoselectivity (Scheme 43). α-Diazo ketones **56** undergo multiple 1,3-dipolar cycloaddition reactions with heterodipolarophiles such as the aldehyde functional groups of 2,4,6-trimethylbenzene-1,3,5-tricarbaldehyde to afford [127] the tris-epoxy-bridged tetrahydropyranone ring system **140** in a chemo- and diastereoselective manner. In turn, these multiple tandem cyclization–cycloaddition

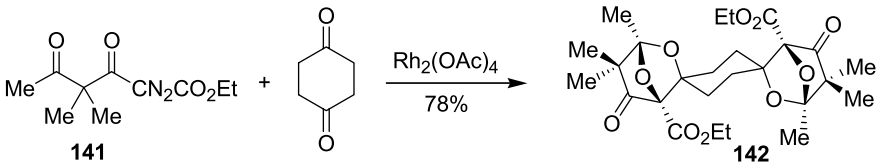


139 **56** **138** **140**

Scheme 43

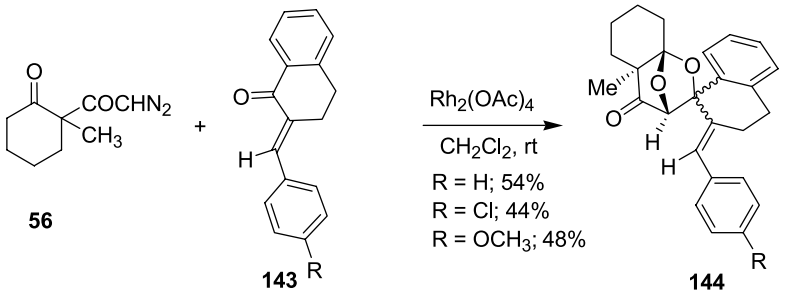
processes, from simple starting materials, provide up to nine new bonds with many stereocenters and with stereoselectivity in a single synthetic operation.

The tandem cyclization–cycloaddition reactions of an α-diazo ketone with di-carbonyl functionalities placed on a flexible framework were performed to afford multiple dioxa-bridged polycyclic system **142** [128]. Interestingly, this reaction furnished the stereochemically favorable cycloadduct with diastereoselectivity and chemoselectivity (Scheme 44).



Scheme 44

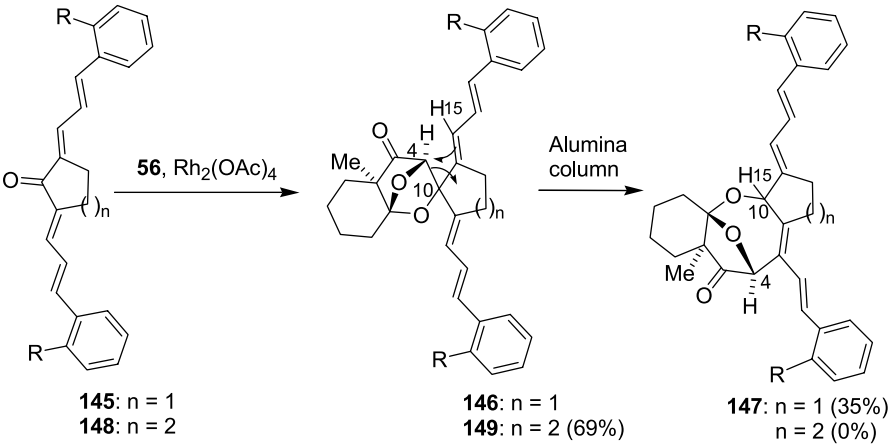
Since the carbonyl ylide dipoles undergo cycloaddition with C=O groups as described above, one would definitely expect a mixture of cycloadducts through both C=C and C=O addition when α,β-unsaturated carbonyl compounds were used as dipolarophiles [129]. Examples have been reported where five-membered ylides react with α,β-unsaturated carbonyl compounds regioselectively at the C=C bond [88, 94]. Chemoselectivity towards C=O cycloaddition can also be achieved, however, in specifically crafted α,β-unsaturated ketones such as arylidenetetralones, bis(arylmethylidene)ketones and bis(heteroarylmethylidene) ketones. The reaction of α-diazo ketone **56** and arylidenetetralones **143** in the presence of $Rh_2(OAc)_4$, for example, led [130] to the spirodioxa ring systems **144** with high regio- and chemoselectivity (Scheme 45). The product **144** is obtained as a diastereomeric mixture (2 : 3) and no C=C bond addition product was observed.



Scheme 45

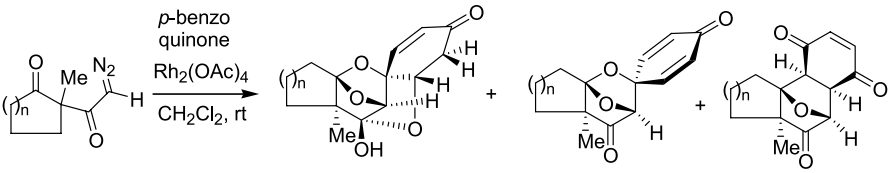
Another interesting example of chemoselective carbonyl ylide cycloaddition is the rhodium(II)-mediated reaction of **56** with the bis(phenylallylidene)cyclopentanone **145** which furnished the novel 2,5-epoxycyclopenta[*b*]-

oxocin-4(5*H*)-ones **147**. Fascinatingly, this process involves the tandem cyclization–cycloaddition-ring expansion reactions. Similarly, reaction of the α-diazo ketone **56** with the bis(phenylallylidene)cyclohexanone **148** afforded the spiro-dioxa-bridged ring system **149** (Scheme 46) with complete regio- and chemoselectivity in good yield [131].



Scheme 46

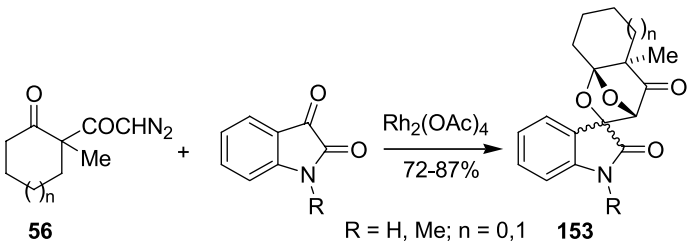
Another example of α,β-unsaturated carbonyl compounds is provided by *p*-quinones. Carbonyl ylides engage *p*-quinones in a manner reminiscent of their reaction with α,β-unsaturated carbonyl compounds [97, 132]. For example, the reaction of **56** with *p*-benzoquinone yielded to the novel oxa-bridged polycyclic systems **150–152** through stereoselective C=O and C=C bond additions (Scheme 47). The formation of **150** through tandem cyclization–cycloaddition-Michael addition is quite interesting as four C–O bonds and one C–C bond are formed in a single synthetic step [133].



Scheme 47

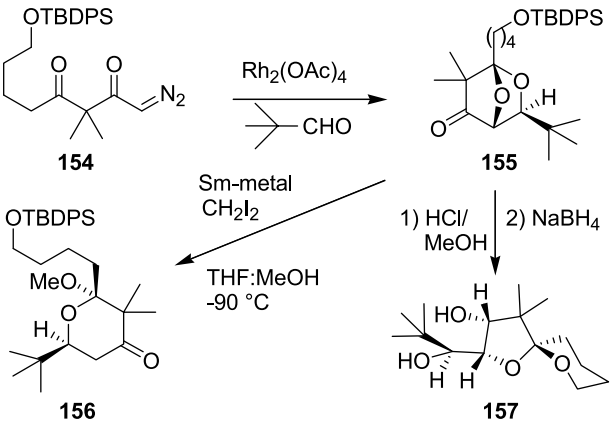
The reaction of **56** with 1,2-dicarbonyl compounds like *N*-substituted isatins has been studied [134, 135] and exclusively affords the oxygenated

spiro-oxindoles **153** through regioselective addition on the C_3 carbonyl group (Scheme 48).



Scheme 48

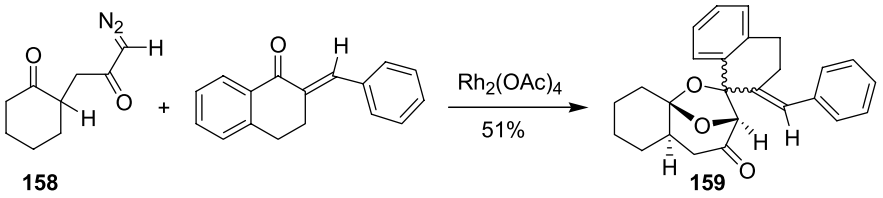
The ring-opening reactions of dioxabicyclo[2.2.1]heptan-5-ones were studied by Winkler and co-workers and used in the synthesis of various oxygen heterocycles [136]. For example, treatment of dioxanorbornanes **155** with samarium iodide as well as with mineral acid led to cyclic hemiketals **156** and spiroketals **157** (Scheme 49).



Scheme 49

Dioxabicyclo[3.2.1]octan-2-ones

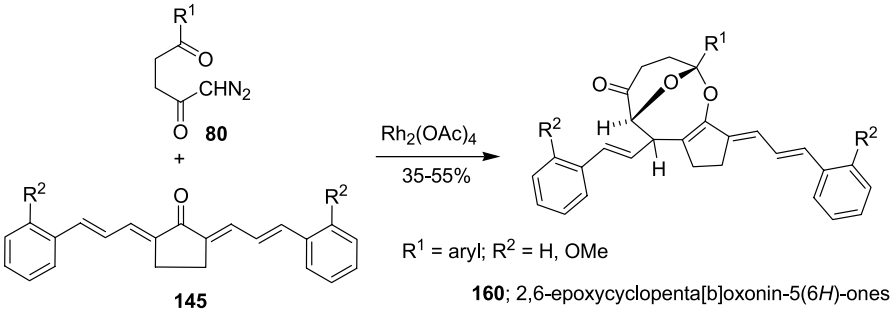
Chemoselective 1,3-dipolar cycloadditions of fused six-membered ring carbonyl ylides with α,β-unsaturated carbonyl compounds have been reported [130]. The spiro-dioxa ring system **159** was obtained by the treatment of the α-diazo ketone **158** with the arylidenetetralone (Scheme 50) in the presence of $Rh_2(OAc)_4$ via exclusive C=O addition in a manner analogous to the five-membered ring carbonyl ylides (see Sect. 2.1).



158 159

Scheme 50

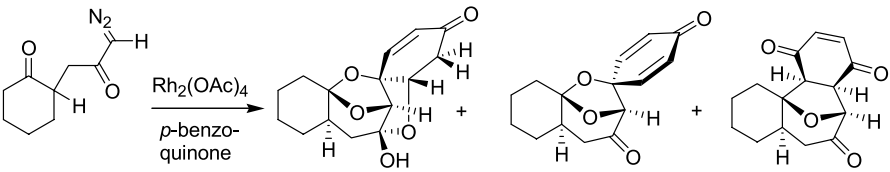
Interestingly, the oxoninone ring system has been synthesized from the rhodium(II)-generated six-membered ring carbonyl ylides [131]. The cycloaddition of six-membered carbonyl ylides derived from **80** to the C=O group of **145** despite the presence of C=C groups behaved anomalously to afford the ring-enlarged products **160** (Scheme 51). This represents an example of the tandem cyclization–cycloaddition-ring enlargement reaction.



80 145

Scheme 51

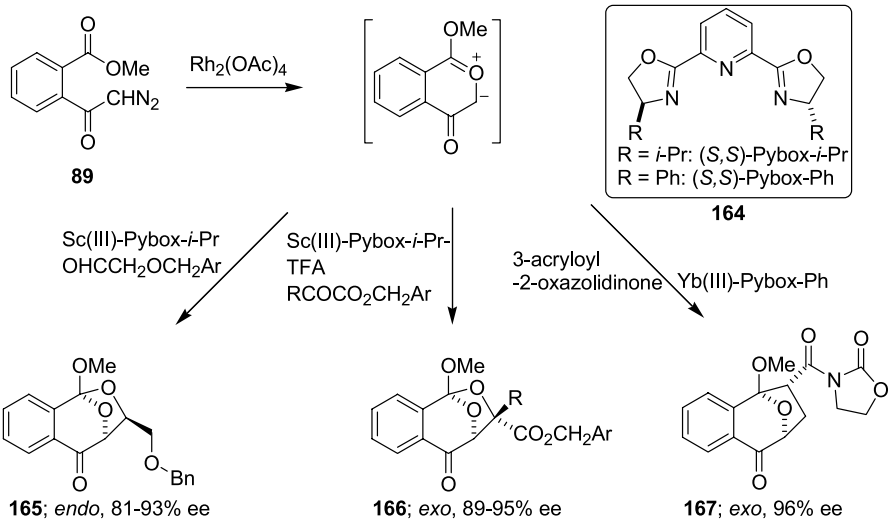
Rhodium-generated bicyclic six-membered ring carbonyl ylides from the diazo ketone **158** with *p*-quinones have also been studied to yield interesting oxygen heterocycles [133]. In line with the five-membered ring carbonyl ylide reactions (see Sect. 2.1), the α-diazocarbonyl compound **158** furnished oxygen-rich heterocyclic systems **161**–**163** (Scheme 52).



158 **161**; 25% **162**; 15% **163**; 5%

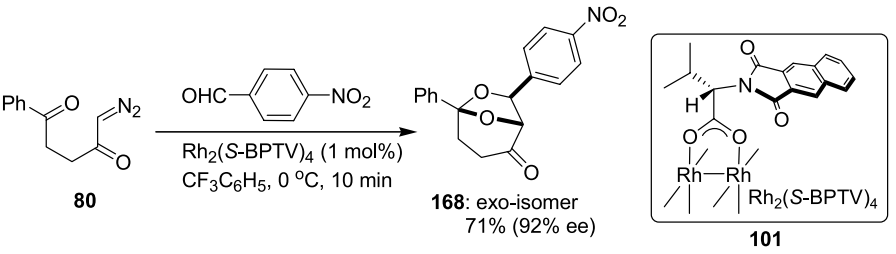
Scheme 52

An enantioselective version of the above reactions has been reported. Lewis acids such as $Yb(OTf)_3$ can profoundly affect the stereochemical outcome of the carbonyl ylide 1,3-dipolar cycloadditions [137]. This provided an indication to effect asymmetric carbonyl ylide cycloaddition using a chiral Lewis acid. The first example of such asymmetric induction using the chiral lanthanide catalysts has been reported [138, 139]. For example, the reaction of diazoacetophenone **89** with benzyloxyacetaldehyde, benzyl pyruvate and 3-acryloyl-2-oxazolidinone in the presence of chiral 2,6-bis(oxazolinyl)pyridine ligands and scandium or ytterbium complexes furnished the corresponding cycloadducts **165–167** with high enantioselectivity (Scheme 53).



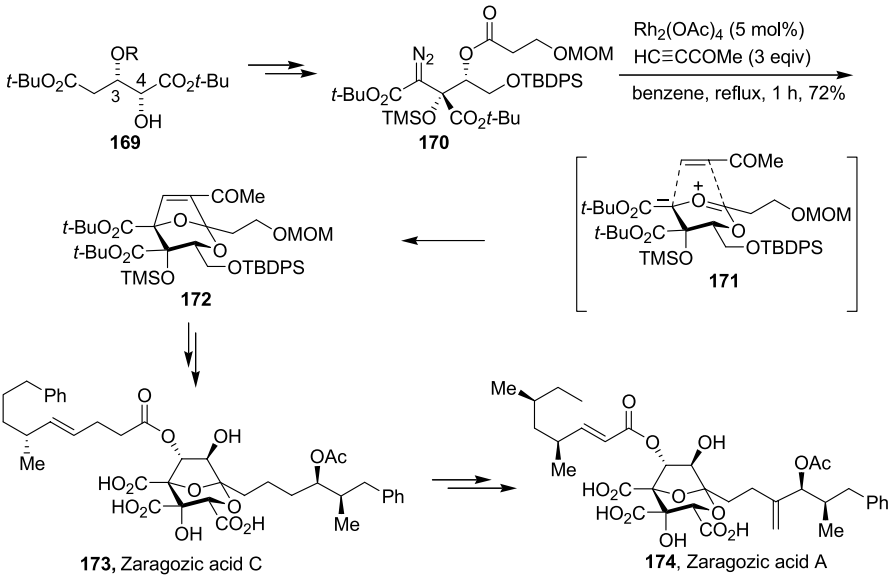
Scheme 53

The highly enantioselective synthesis of dioxabicyclo[3.2.1]octan-2-ones was achieved using Rh_2(*S*-BPTV)$_4$ **101**. The cyclization–cycloaddition reaction of **80** with *p*-nitrobenzaldehyde in the presence of **101** provided exclusively *exo* cycloadduct **168** (Scheme 54) with 92% ee [140].



Scheme 54

The dioxabicyclo[3.2.1]octan-2-one ring system is present in natural products, namely brevicomins and zaragozic acids. Application of tandem cyclization–cycloaddition methodology to the total synthesis of *exo*- and *endo*-brevicomin has been carried out [129]. A carbonyl ylide-based approach towards the bicyclic core of the zaragozic acids/squalestatins, a potent inhibitor of squalene synthase, has been reported [141–143]. A recent study on a highly convergent and stereocontrolled total synthesis [144, 145] of zaragozic acid C (**173**) in 30 steps (longest linear sequence) and 3.7% overall yield from di-*tert*-butyl D-tartrate **169** has been described. Further manipulations of zaragozic acid C have furnished the more complex ring structure of zaragozic acid A (**174**). The synthesis illustrates the power of the carbonyl ylide cycloaddition methodology for rapidly assembling the desired core system from α-diazo ester **170** and a suitable 3-butyn-2-one as a dipolarophile under the influence of a Rh(II) catalyst in a single step to provide the unique 2,8-dioxabicyclo[3.2.1]octane **172** (Scheme 55).

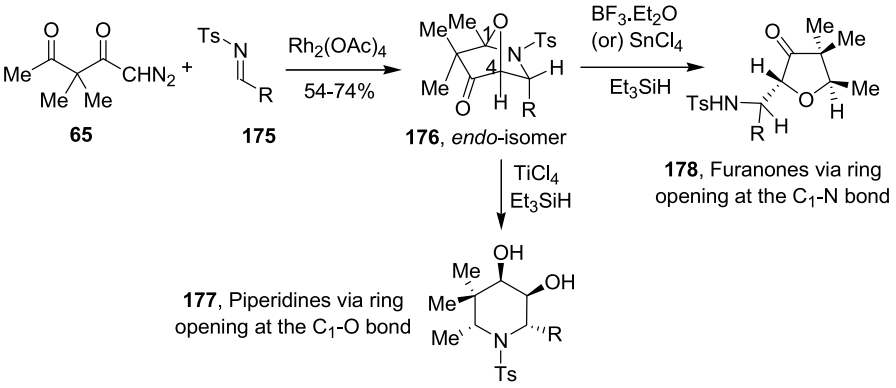


Scheme 55

3.3 Synthesis of Oxazabicyclo[2.2.1]heptan-5-ones and Oxazabicyclo[3.2.1]octan-2-ones

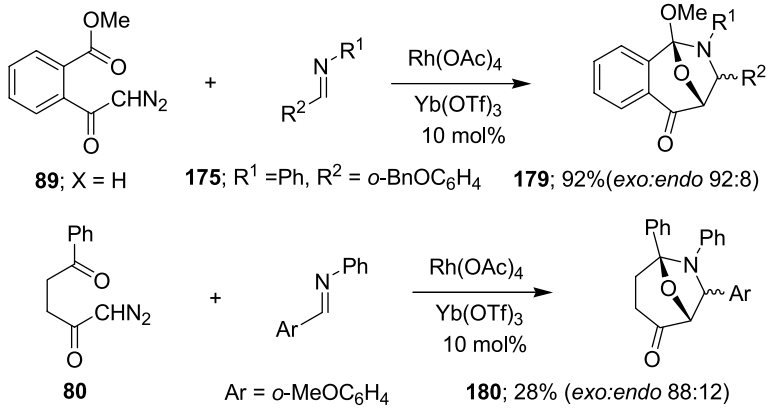
Oxazabicyclo[2.2.1]heptan-5-one ring systems were constructed via the cycloaddition of carbonyl ylides with imines. Muthusamy and co-workers have

reported a facile catalytic route to construct oxazabicyclo[2.2.1]heptan-5-one ring systems using *N*-tosylimines [146]. Reaction of diazo ketones **65** with *N*-tosylimines **175** afforded the functionalized oxazabicyclo[2.2.1]heptan-5-ones **176** in a highly stereoselective manner. The regio- and chemoselective reductive ring-opening reaction of **176** was performed using various Lewis acids [147]. The selective ring opening occurs at the C_1–O bond in the presence of $TiCl_4$ and at the C_1–N bond with other Lewis acids, furnishing dihydroxypiperidines **177** and furanones **178**, respectively (Scheme 56).



Scheme 56

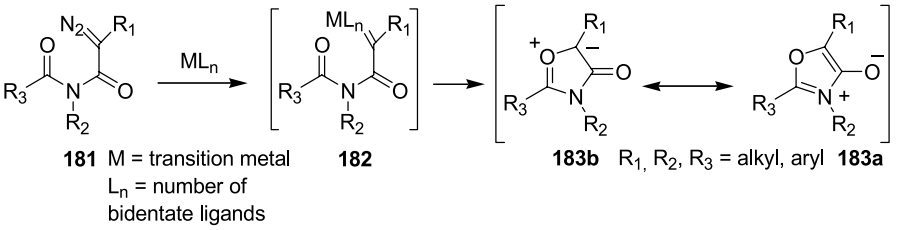
Suga and co-workers have studied [148] the effect of several Lewis acids in cycloadditions. $Yb(OTf)_3$ was found to be effective in promoting the 1,3-dipolar cycloaddition reactions of six-membered ring carbonyl ylides derived from **89** or **80** with imines. In the absence of Lewis acid, no cycloaddition reaction occurred (Scheme 57).



Scheme 57

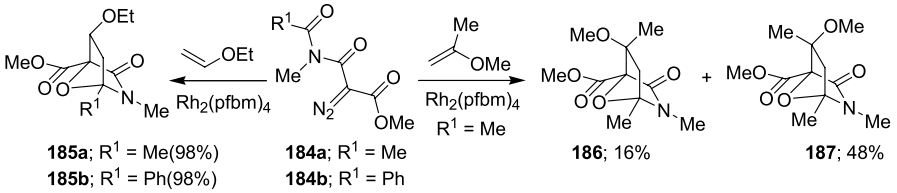
3.4
Synthesis of Oxazabicyclo[2.2.1]heptan-3-ones

The decomposition of suitably crafted diazoimides **181**, in the presence of a transition metal catalyst, affords the metallo-carbenoids **182** that undergo intramolecular cyclization onto the neighboring amide carbonyl oxygen to form the five-membered ring carbonyl ylides (isomünchnones) **183** (Scheme 58). Early examples of inter- and intramolecular 1,3-dipolar cycloaddition of the mesoionic ylides **183** have mainly emanated from the research groups of Ibata [149], Maier [150] and Padwa [151]. These reactive species (isomünchnones) can be trapped by various electron-rich and electron-deficient dipolarophiles [152] to furnish the cycloadducts in high yield. Much work has been reported in this area and for clarity of presentation is described here under various subheadings.



Scheme 58

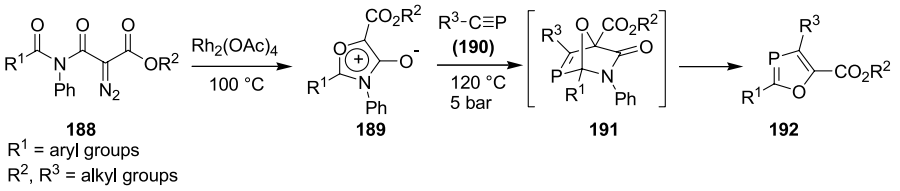
The formation of oxazabicyclo[2.2.1]heptan-3-one ring systems has been demonstrated via the diastereoselective cycloaddition of a variety of unsymmetrical, monoactivated alkenes with isomünchnones [153]. The reaction of the α-diazoimides **184a,b** with ethyl vinyl ether in the presence of $Rh_2(pfbm)_4$ as the catalyst afforded the cycloadducts **185a,b** with diastereoselectivity (Scheme 59). Further, the reaction of the diazoimide **184a** with 2-methoxypropene, an *ipso*-substituted vinyl ether, was studied to evaluate whether the above-observed stereoselectivity was steric or electronic in nature. The observation of a 1:3 *exo/endo* ratio of the diastereomers **186** and **187** from the reaction at a relatively high temperature (130 °C) and a pro-



Scheme 59

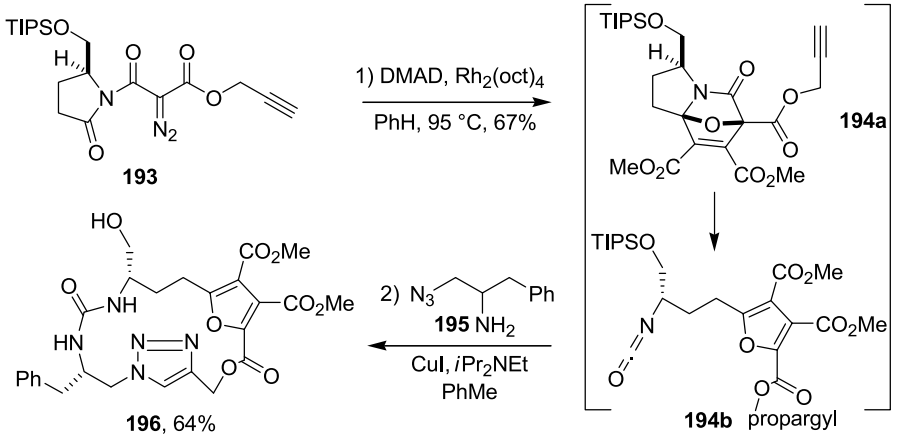
longed exposure (8 h) indicated a dramatic decrease in the reaction rate and indicated the existence of a large HOMO–LUMO gap that supported a steric contribution to the diastereoselectivity.

The reaction of isomünchnones with phosphaalkynes has been reported as a novel route to 1,3-oxaphospholes [154]. Isomünchnones **189**, derived from **188**, were treated with phosphaalkynes **190** in a pressure-Schlenk tube under 5 bar pressure to afford the 1,3-oxaphospholes **192** in a regiospecific manner (Scheme 60). The bicyclic intermediates **191** are presumably formed via a 1,3-dipolar cycloaddition process and apparently decompose immediately in a retro-Diels–Alder reaction to furnish the 1,3-oxaphospholes **192.** On consideration of the charge distribution in the isomünchnone system and the polarity of the P≡C triple bond, the regiochemistry of this 1,3-dipolar cycloaddition is rather surprising and it is clear that this 1,3-dipolar cycloaddition does not proceed under charge control.



Scheme 60

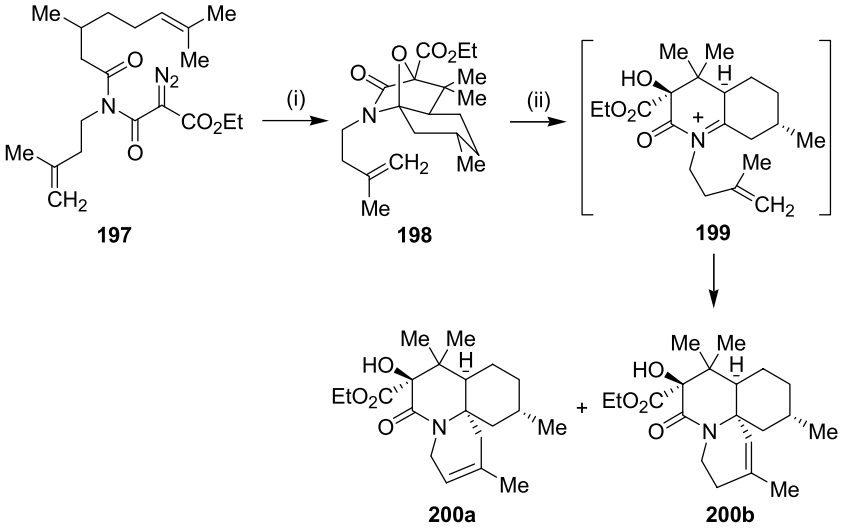
Schreiber and co-workers have reported [155] that reactions of the Cu(I)-catalyzed macrocycloaddition of alkynes with azides appear to provide a robust method for the synthesis of macrocyclic triazole **196** (Scheme 61). In



Scheme 61

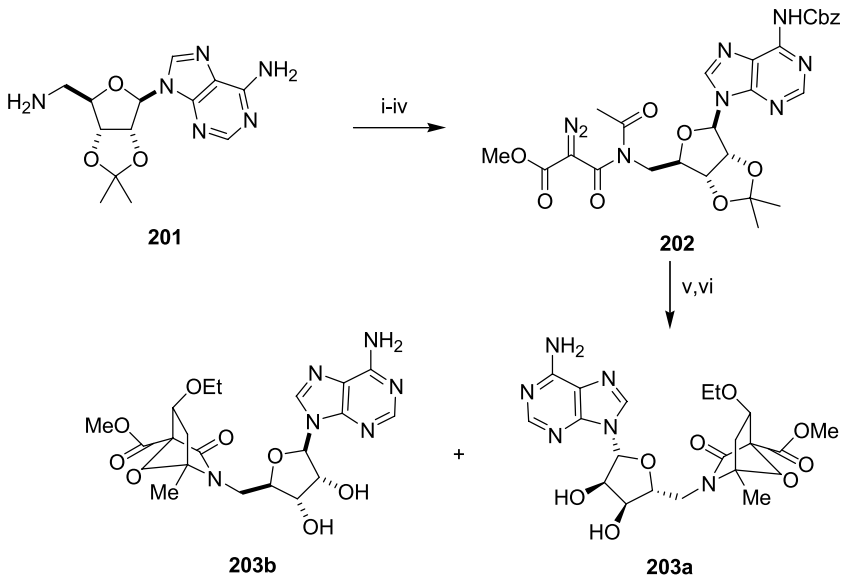
this case, decomposition of diazoimide **193** with $Rh_2(oct)_4$ initiates a cascade reaction to yield an indolizinone **194a** that then undergoes a [4+2] cycloreversion reaction releasing an isocyanate **194b**. The addition of (*S*)- or (*R*)-azidomethylphenylalanine (**195**), followed by the treatment with CuI afforded the macrocycle **196** efficiently.

The construction of polyheterocyclic ring systems has been demonstrated based on the potential use of the tandem carbenoid cyclization–cycloaddition–Mannich cyclization reaction of diazoimides [156]. The construction of a more complex nitrogen heterocyclic system, particularly the B-ring homologues of the erythrinane family of alkaloids, can be easily achieved by incorporating an internal nucleophile on the tether. An interesting example of the sequential cycloaddition–π-cyclization process is shown with the diazoimide **197**, obtained from citronellic acid. The reaction of the diazoimide **197** with $Rh_2(pfb)_4$ generated the isomünchnone dipole, which underwent an intramolecular cycloaddition with one of the tethered alkenes to give oxazabicyclo[2.2.1]heptan-3-one **198** in good yield (Scheme 62). Successive treatment of the cycloadduct **198** with $BF_3 \cdot 2AcOH$ furnished a 4:1 mixture of lactams **200a**,**b** via the formation of the *N*-acyliminium ion **199** [157].



Scheme 62 (i) $Rh_2(pfb)_4$; (ii) $BF_3 \cdot 2AcOH$

An isomünchnone-based strategy has also been deployed to gain access to a new class of 5-functionalized adenosines [158]. Elaboration of the 5′-aminoadenosine **201** employing amine protection, amide formation with methyl malonyl chloride and the usual diazotransfer reaction led to the α-diazoimide **202**. The $Rh_2(pfbm)_4$-catalyzed reaction of the diazoimide **202** in the presence of ethyl vinyl ether yielded the *endo*-selective cycloadducts **203a**

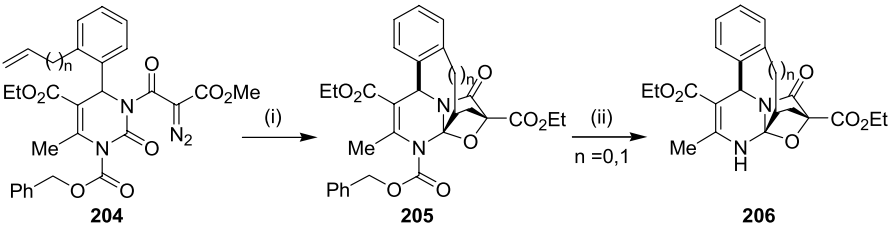


Scheme 63 (i) $(CH_3CO)_2O$, pyridine; (ii) Rapoport's reagent; (iii) methyl malonyl chloride; (iv) MsN_3, Et_3N; (v) ethyl vinyl ether, $Rh_2(pfbm)_4$, PhCl, 130 °C, 98%; (vi) TFA/H_2O 10:1; Pd/C, EtOH, NH_4CO_2H

and **203b** as a 1:1 mixture of diastereomers with the facial bias imposed by the chiral ribose moiety present in adenosine (Scheme 63).

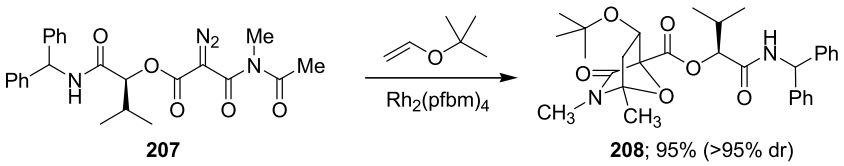
Kappe and co-workers have extended their intermolecular isomünchnone cycloaddition reaction (see Scheme 26) to an intramolecular version to obtain the conformationally rigid polyheterocycles **206**, which mimic the putative receptor-bound conformation of dihydropyrimidine-type calcium channel modulators [159]. The key step in the synthesis involves the regio- and diastereoselective intramolecular 1,3-dipolar cycloaddition reaction of a dihydropyrimidine-fused isomünchnone dipole. The diazoimides **204** were readily prepared by *N*-malonyl acylation of the corresponding pyrimidones, followed by a standard diazotransfer and Cbz protection reactions. Decomposition of the Cbz-protected diazoimides **204** with a catalytic amount of $Rh_2(OAc)_4$ furnished the pentacyclic dihydropyrimidine systems **205** (Scheme 64) without the isolation of the initially generated transient isomünchnone dipoles [160]. The removal of the Cbz group by the catalytic hydrogenation method provided the desired conformationally rigid dihydropyrimidine **206** in high yield.

Asymmetric versions of the intermolecular cycloaddition of isomünchnone dipoles, further enhancing the synthetic appeal of this cycloaddition protocol, have been developed. Austin and co-workers have reported [161] the optimization of a chiral auxiliary for the diastereofacially selective 1,3-dipolar cycloaddition of isomünchnones in the presence of a variety of vinyl



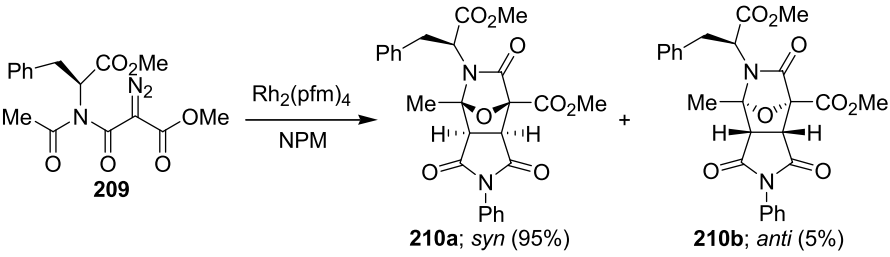
Scheme 64 (i) $Rh_2(OAc)_4$; (ii) H_2, 10% Pd/C, rt, 1 atm

ethers. The diastereomeric ratio (dr) obtained with the optimized auxiliary exceeds 95% and the auxiliary is efficiently removed from the cycloadducts through an unusually facile ester aminolysis. Treatment of the α-diazoimide **207** with $Rh_2(pfbm)_4$ as the catalyst in the presence of *tert*-butyl vinyl ether, for example, led to the formation of the cycloadduct **208** (95% dr) (Scheme 65). The same group has demonstrated the above methodology for solid-phase synthesis using a benzhydrylamine (BHA) resin and a novel and chemoselective resin cleavage process has been described [162].



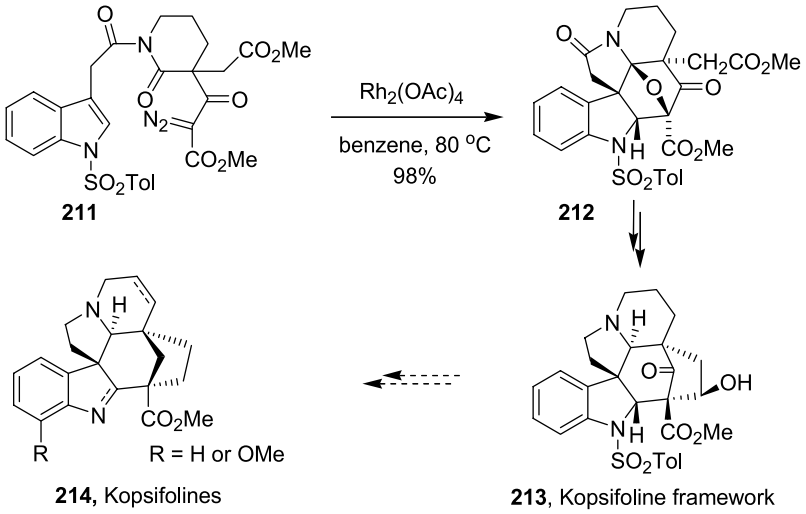
Scheme 65

Stereocontrolled [3+2]-cycloadditions using various amino acid-derived chiral isomünchnone dipoles provide access to the enantiopure cycloadducts [163]. Decomposition of the amino acid-derived diazoimide **209** with rhodium(II) perfluorobutyramidate $[Rh_2(pfm)_4]$ in the presence of NPM resulted in the formation of the cycloadducts **210a** and **210b** with nearly complete *exo*/*endo* selectivity and high π-facial selectivity (Scheme 66).



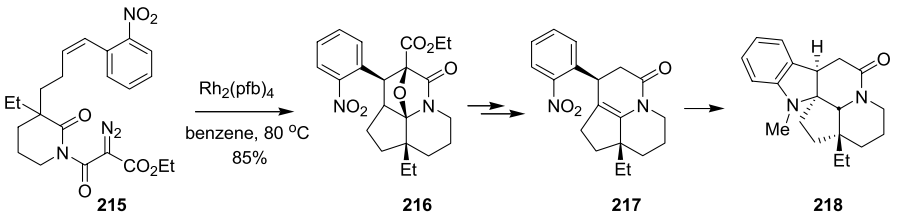
Scheme 66

Oxazabicyclo[2.2.1]heptan-3-one ring systems have significant potential for the synthesis of many alkaloids. The hexacyclic framework of the kopsifoline alkaloids based on a Rh(II)-catalyzed cyclization–cycloaddition cascade has been demonstrated by Padwa et al. [164–166]. The reaction of diazoimide **211** with catalytic $Rh_2(OAc)_4$ under reflux conditions afforded cycloadduct **212** in 90% yield. Further functional group transformations of **212** led to hexacyclic system **213** that contains the complete skeleton of the kopsifoline **214** (Scheme 67).



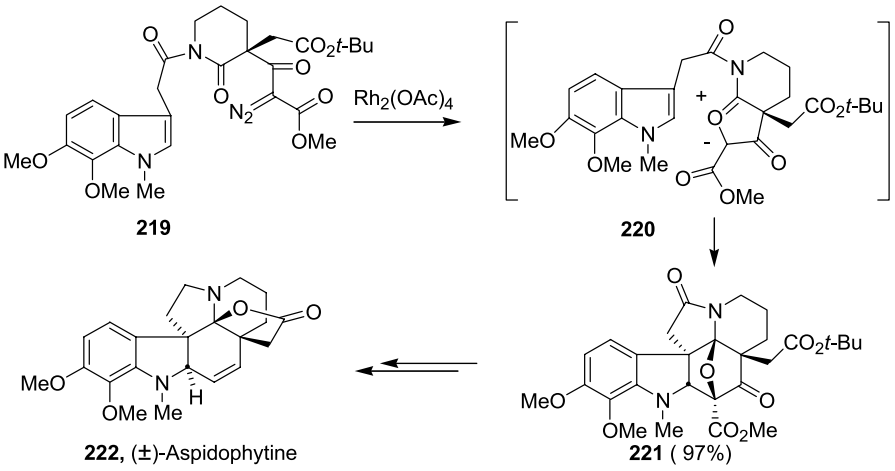
Scheme 67

A formal synthesis of (±)-vallesamidine (**218**) has been achieved [167] based on an intramolecular dipolar cycloaddition reaction of isomünchnone. Following a study of a range of model substrates, the reaction of the cyclic diazoimide **215** with $Rh_2(pfb)_4$ was carried out to obtain the desired cycloadduct **216** as a single diastereomer (Scheme 68). A series of functional group maneuvers on **216** afforded the enamide **217**, which can be readily elaborated to (±)-vallesamidine (**218**) using a known methodology [168].



Scheme 68

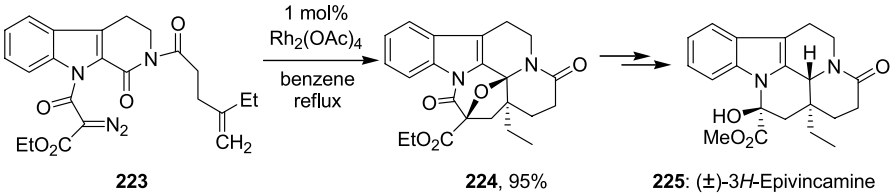
As an extension of the above methodology, the intramolecular cycloaddition of isomünchnone dipoles across an indole double bond has been investigated. This reaction has been shown by Padwa and co-workers to provide a facile entry into the pentacyclic skeleton of the aspidosperma alkaloids [157, 169]. For example, the synthesis of aspidophytine has been developed based on the rhodium-catalyzed cyclization-dipolar cycloaddition sequence [170]. The push-pull carbonyl ylide dipole **220** was derived by reaction of α-diazoimide **219** in the presence of $Rh_2(OAc)_4$ catalyst. Subsequent intramolecular cycloaddition across the tethered indolyl group furnished cycloadduct **221**. The bulky *tert*-butyl ester functionality blocks the *endo* approach thereby resulting in cycloaddition exclusively taking place from less-congested *exo* face and leads to *exo*-cycloadduct **221**. The tandem cyclization–cycloaddition sequence is attractive as four stereocenters are formed with a high degree of stereocontrol and further functional group manipulations of **221** afforded the pentacyclic skeleton of the aspidophytine **222** (Scheme 69).



Scheme 69

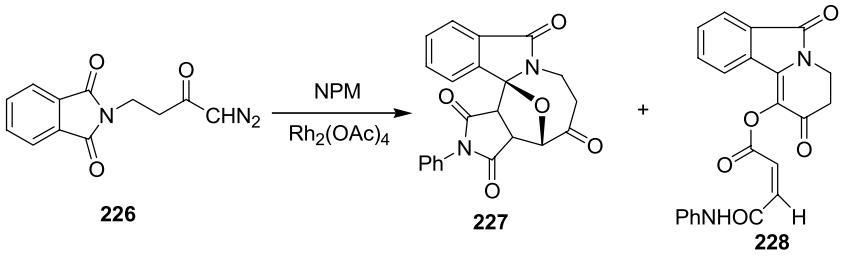
A concise synthesis of biologically important *Vinca* alkaloid (±)-3*H*-epivincamine was accomplished. A central step in the synthesis consists of rhodium-catalyzed intramolecular [3+2]-cycloaddition of α-diazo amide **223** which provides the cycloadduct **224**, which has the core skeleton of the natural product, in excellent yield with complete diastereoselectivity (Scheme 70). Further, a reductive ring opening of the cycloadduct followed by a decarboethoxylation reaction and a base-induced keto-amide ring contraction reaction furnished (±)-3*H*-epivincamine (**225**) [171].

Seven-membered ring carbonyl ylides derived from phthalimides can also participate in these tandem cyclization–cycloaddition reactions, the $Rh_2(OAc)_4$-catalyzed reaction of 1-diazo-4-phthalimidobutanone (**226**) pro-



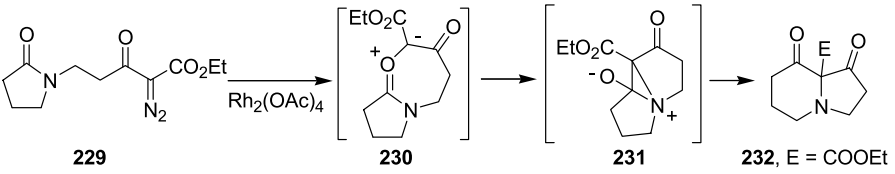
Scheme 70

ceeding quite smoothly with DMAD and NPM [172]. When *N*-phenylmaleimide was used as the trapping agent, the 9-oxa-2-azabicyclo[4.2.1]nonan-5-one **227** (45%) was obtained as the major product, along with **228** (Scheme 71).



Scheme 71

A range of cyclic diazo ketoamides have been studied by Padwa and co-workers to generate seven-membered carbonyl ylides [172]. The Rh(II)-catalyzed reaction of the amido diazo ketoester **229** was found to cleanly afford the rearranged indolizidone **232** via the intermediates **230** and **231** (Scheme 72).



Scheme 72

4 Conclusion

As can be gleaned from the forgoing examples, interest in the explorations with carbonyl ylides provides a unique opportunity to accomplish a var-

iety of mono- and bicyclic heterocycles via both intra- and intermolecular reactions. The possibility of rapid generation of compounds possessing molecular complexity and diversity with good stereo- and regiocontrol make this rhodium-mediated tandem cyclization–cycloaddition approach an economical, effective and efficient synthetic strategy. While concise and stereoselective syntheses of many complex natural products, particularly terpenoids and alkaloids, have been accomplished, there are many more targets where the carbonyl ylide-based strategy can be effectively harnessed. Many exciting prospects, particularly with regard to the development of an asymmetric version and combinatorial variants of these reactions are going to sustain the ongoing interest in the carbonyl ylide-based tandem cyclization–cycloaddition chemistry.

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Heterocycles from Unsaturated Phosphorus Ylides

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Abstract Phosphacumulene ylides of the general formula $Ph_3P{=}C{=}C{=}X$ [X=O, S, NR, $(OR)_2$] are versatile C_2-building blocks. They can act either as C-nucleophiles-only in a manner typical of phosphorus ylides, or as cumulenes undergoing [2 + *n*]-cycloadditions with other cumulenes such as CO_2, COS, RNCO etc. Most prominent is their tandem addition–Wittig alkenation of hydroxy- or amino-substituted carbonyl compounds. With aptly chosen reaction partners all these pathways may lead to heterocyclic products. Some recent applications of these methods to the syntheses of azetidines, five-membered lactams, lactones, tetramates, tetronates and pyrroles as well as to six-membered quinolones and to macrolides are delineated.

Keywords Phosphorus ylides · Phosphacumulenes · Tetronates · Tetramates

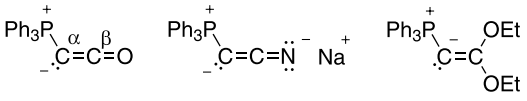
Abbreviations

aq.	Aqueous
Bn	Benzyl
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DMAP	4-(Dimethylamino)pyridine
ee	Enantiomeric excess
equiv	Equivalent
LDA	Lithium diisopropylamide
mesylate	Methanesulfonate
μw	Microwave irradiation

Ms	Methanesulfonate
NaHMDS	Sodium hexamethyldisilazanide
NMR	Nuclear magnetic resonance (spectroscopy)
SEM	[2-(Trimethylsilyl)ethoxy]methyl
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TMSE	Trimethylsilylethyl
Tos	Toluenesulfonyl
Tr	Triphenylmethyl (trityl)

1 Introduction

Alkylidenephosphoranes (a.k.a. phosphorus ylides) of the general formula $Ph_3P{=}CR^1R^2$ (**1**) have been frequently used in key steps of heterocycle synthesis. Numerous papers and review articles [1–4] testify their versatility in the construction of rings with sizes ranging from three to well beyond 20 and with virtually any number, kind and distribution of heteroatoms. The Wittig alkenation of carbonyl groups is doubtless the most common, though not the only, reaction of P-ylides that has been employed in the cyclization of bifunctional precursors. The cycloaddition between acyl ylides (**1**: R^1 = H, R^2 = CO–R) and azides to give 1,2,3-triazoles [5, 6] and the S_N2-type ring-closure of ω-halo-ylides [7–10] are noteworthy non-Wittig approaches. In any case, the reactivity of the used phosphorus ylide is decisive for the range of accessible target ring sizes and functionalities. Virtually all classes of ylides, bar the least reactive ones bearing two electron-withdrawing groups R^1, R^2, have been successfully applied to heterocycle synthesis. This chapter deals with the possibilities and benefits of using ylides with a carbon–carbon double bond as part of the ylidic α-carbon atom of **1**. They are customarily referred to as cumulated ylides or phosphacumulenes and feature unique electronic and structural properties that give rise to a chemistry quite distinct from that of ylides **1** carrying three substituents on C^α. Figure 1 depicts three typical derivatives that were frequently used in the construction of heterocyclic systems. Many more are known [11, 12].



2 **3** **4**

Fig. 1 Phosphacumulenes: (triphenylphosphoranylidene)ketene (**2**), sodium cyanomethylenetriphenylphosphorane (**3**), and (diethoxyvinylidene)triphenylphosphorane (**4**)

(Triphenylphosphoranylidene)ketene ($Ph_3P{=}C{=}C{=}O$) **2** has been widely utilized as a C_2-building block in organic and organometallic chemistry. It can be prepared in three steps from methyl bromoacetate and triphenylphosphane [13, 14] as a fairly air-stable crystalline solid. Recently, a variant of ylide **2** immobilized on a polystyrene resin also became available [15]. Despite its ketene-like structure, ylide **2** is not prone to dimerization and, untypical of phosphorus ylides, does not normally enter into Wittig olefination reactions with carbonyl compounds. However, with acidic compounds such as alcohols, amines, thiols or even CH-acidic 1,3-dicarbonyl compounds it reacts rapidly to give the corresponding stabilized acyl ylides by a formal addition across its C=C double bond. As these acyl ylides are more Wittig-active than Ph_3PCCO, bifunctional compounds containing both a carbonyl and an acidic group react with **2** to give unsaturated heterocycles. Ylide **2** can also undergo cycloaddition and insertion reactions with other heteroallenes such as isocyanates to furnish neutral four- or six-membered heterocyclic phosphoranes.

The thio analog of **2**, Ph_3PCCS, is too unreactive for most synthetic applications while the aza analogs Ph_3PCCNR offer too little genuine chemistry over that of **2** to justify their relatively cumbersome synthesis and handling. One exception is the anionic ylide **3**, which is a strong nucleophile, readily available by deprotonation of the stabilized cyano ylide $Ph_3P{=}CH{-}CN$. Depending on conditions and electrophilic partners, the ylide anion **3** can react via its C^{α}- or via its N-atom [16].

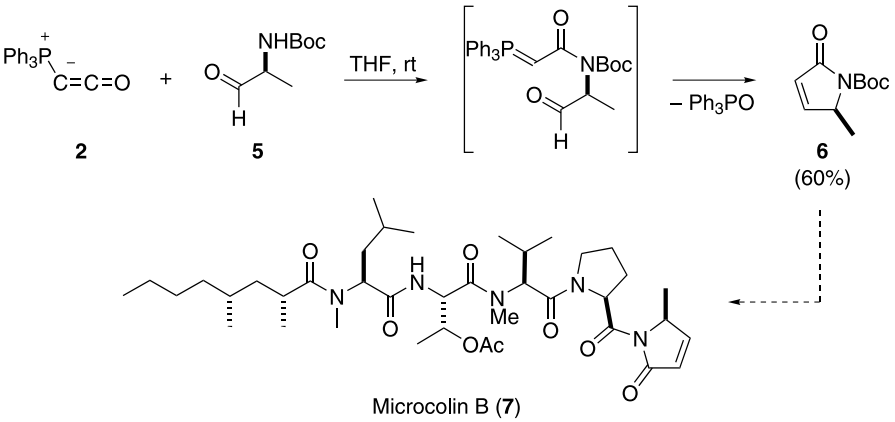
The formal acetals of ketene **2**, e.g. (diethoxyvinylidene)triphenylphosphorane **4**, are highly reactive and, like **2**, add all sorts of H–X compounds such as carboxylic acids, alcohols, amines, 1,3-dicarbonyls etc. across their C=C bond. Heterocycles result from cycloadditions of these ylides to heteroallenes [17].

2
Heterocycles from $Ph_3PC{=}C{=}O$ and Bifunctional Carbonyl Compounds

2.1
Butenolides and γ-Butyrolactams

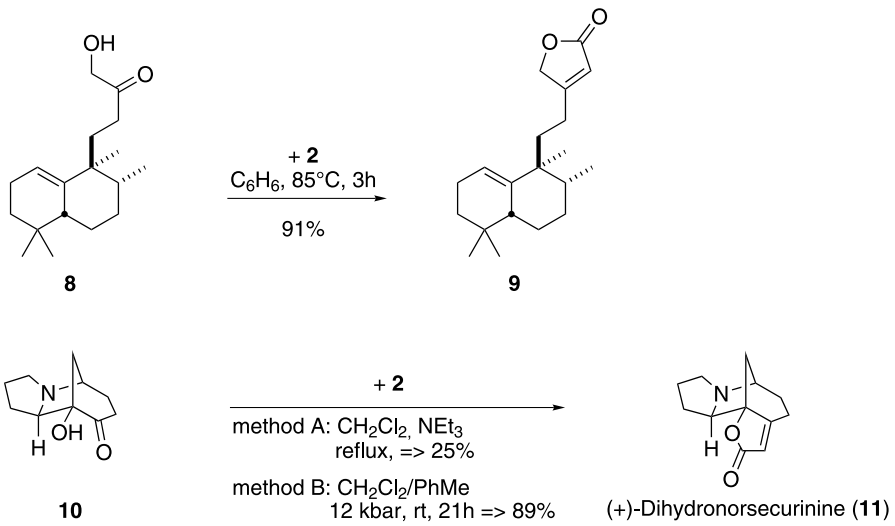
Cumulated ylides enter into domino addition–intramolecular Wittig olefination reactions with α- and β-hydroxy or amino aldehydes and ketones to afford unsaturated five- and six-membered oxacycles or azacycles, respectively. In this way *o*-hydroxyaryl aldehydes were converted with **2** into the corresponding annulated pyrans, while pyrrolizines were obtained from 2-acylpyrroles [18]. Further applications of this approach have been reported more recently. Andrus et al. [19] prepared the enantiomerically pure pyrrolenone **6** by reaction of ylide **2** with *N*-Boc protected aldehyde **5** in 60% yield. Plans by this group to use **6** as an intermediate en route to the im-

munosuppressant microcolin B (**7**) produced by the blue-green alga *Lyngbya majuscula* had to be abandoned as the *N*-deprotection of **6** proceeded with racemization (Scheme 1).



Scheme 1

The addition of primary alcohols onto **2** takes place as readily as that of secondary amines. For instance, Marcos et al. [20] built up the natural halimanolide **9** as occurring in *Polyalthia langifolia* by cyclizing the corresponding alcohol **8** with ylide **2** (Scheme 2, top). A similar butenolide was prepared likewise by Nishiyama et al. [21]. Tertiary alcohols generally require

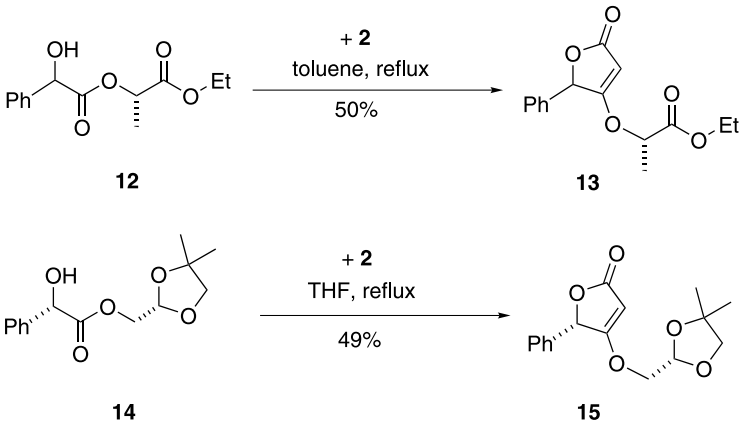


Scheme 2

more drastic conditions to add to ylide **2** due to steric hindrance and low nucleophilicity of the –OH group. α-Hydroxyketones are particularly hard to cyclize when the product butenolide is part of a strained framework. This was demonstrated by Weinreb's [22] synthesis of the *Securinega* alkaloid (+)-14,15-dihydronorsecurinine (**11**) from hydroxyketone **10.** While conventional thermal conditions afforded a meagre 25%, almost 90% of **11** was obtained in the autoclave at 12 kbar and room temperature. Which step, addition or Wittig cyclization, benefitted more from the increase in pressure remains open (Scheme 2, bottom).

2.2 Macrolides

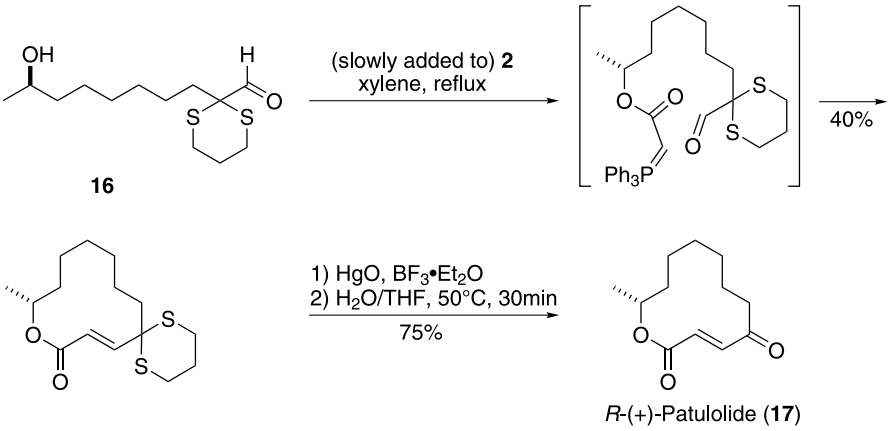
Long-chain ω-hydroxyaldehydes can be cyclized to give (*E*)-α,β-unsaturated macrocyclic lactones ("macrolides") by slow addition to solutions of ylide **2** in hot toluene, xylene or THF [23]. High-dilution conditions are not required as only the intermediate ester ylides, the concentration of which is kept low by slow addition of the hydroxyaldehyde, can undergo a ring-closing Wittig alkenation. Yields typically range from 40 to 80% for ring sizes of 11 to 24. Functional groups such as esters like **12**, olefins and susceptible protective groups e.g. acetals **14** are not affected under these mild conditions (Scheme 3) [24].



Scheme 3

The method had been successfully applied to the synthesis of natural musk lactones, e.g. recifeiolide [25], as well as antibiotics such as A 26771B [26] and (–)-grahamimycin [27]. Further examples were published in the mid-1990s.

The antibiotic *R*-(+)-patulolide (**17**), first isolated in 1985 from the culture broth of *Penicillium urticae* mutant S11R59, was obtained from hydrox-

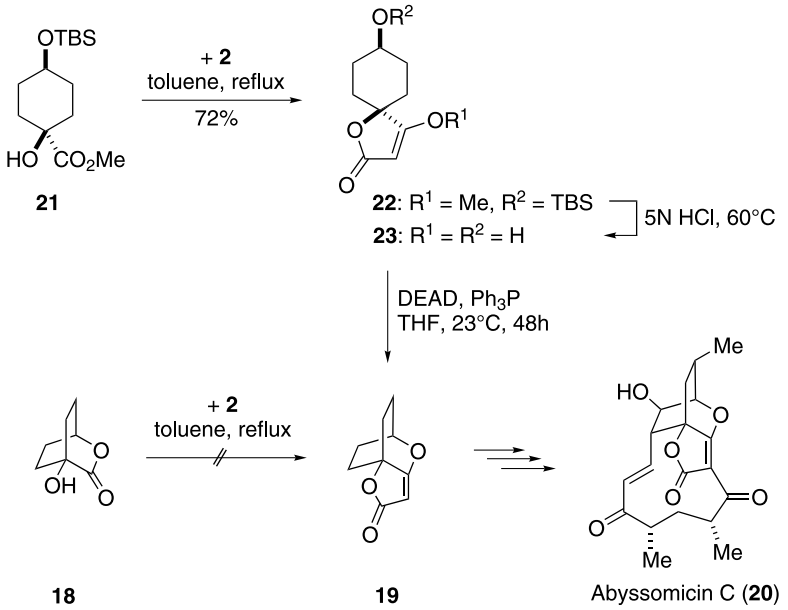


Scheme 4

yaldehyde **16** in 30% overall yield (Scheme 4) [28]. Unlike analogous 14- or 16-membered rings [23], the 12-membered ring of undec-2-enolides seems to adopt a conformation not amenable to downstream oxidation of the γ-position with selenium dioxide. Hence, the γ-keto group of **17** had to be introduced in a masked form with the acyclic precursor **16.** The same group also reported the syntheses of three enantiomerically pure α-methyl substituted 13- to 15-membered saturated musk macrolides that had previously been isolated from the resin of *Ferula galbaniflua* [29].

2.3
Tetronates and Tetramates

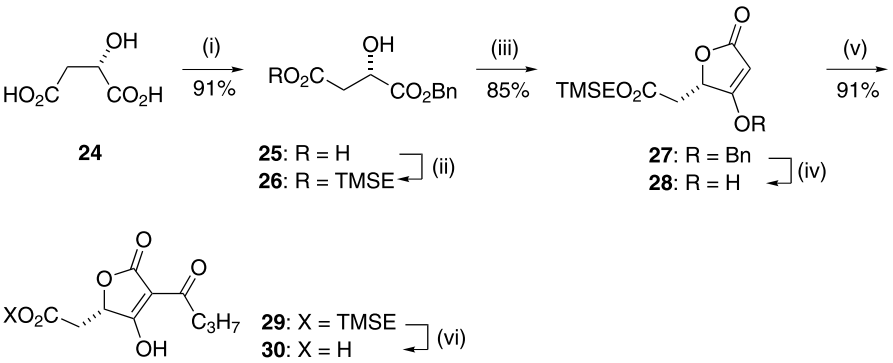
Due to the intramolecular nature of the Wittig olefination step, even esters of α-hydroxy, α-amino or α-sulfanyl carboxylic acids react with ylide **2** to yield the corresponding tetronates, tetramates or thiotetronates [30]. Again, other more remote ester groups or acetals, aldehydes etc. may be present and are not affected. However, the reaction normally requires harsher conditions (such as refluxing in THF) than cyclization of the corresponding aldehydes or ketones. For instance, Maier et al. [31] were unable to convert the tertiary α-hydroxyester **18**, which bears some resemblance to hydroxyketone **10**, into the tricyclic tetronate **19**, a valuable intermediate en route to the natural antibiotic abyssomicin C (**20**) (Scheme 5). Because high-pressure conditions, as in the synthesis of **11**, were not applied to **18**, it remains unclear whether the smaller ring or the additional O-atom or both were responsible for this failure. Interestingly, tetronate **19** was accessible by a detour. Reaction of ylide **2** with the monocyclic tertiary α-hydroxyester **21** gave the 5-spirotetronate **22**, which in turn was hydrolyzed to the corresponding tetronic acid **23**. Its intramolecular Mitsunobu esterification finally afforded the desired product tetronate **19**.



Scheme 5

The majority of natural tetronic acids are 3-acyl derivatives that owe their frequently observed high bioactivity to the metal-chelating and phosphate-mimicking properties of this functional group constellation. Quite a few syntheses of such compounds based upon the use of ylide **2** have been reported. In most cases, the 3-acyl residues were introduced after the actual ring-closure step by separate protocols. *S*-Carlosic acid (**30**), an intermediate in the biosynthesis of penicillic acid, was prepared in six steps and 32% yield from L-malic acid (**24**) (Scheme 6) [32]. Its monobenzyl ester **25** was protected at the remaining β-carboxylic acid group as a trimethylsilylethyl (TMSE) ester **26.** The latter was converted with ylide **2** into tetronate **27**, which had to be hydrogenolytically debenzylated to give tetronic acid **28** prior to C-acylation in the 3-position according to the so-called Yoshii protocol [33], i.e. by adding butyric acid, DCC, DMAP and NEt_3. The 3-acyltetronate **29**, which was obtained in excellent 91% yield, was finally deprotected with TBAF to set free carlosic acid 5*S*-(–)-**30.**

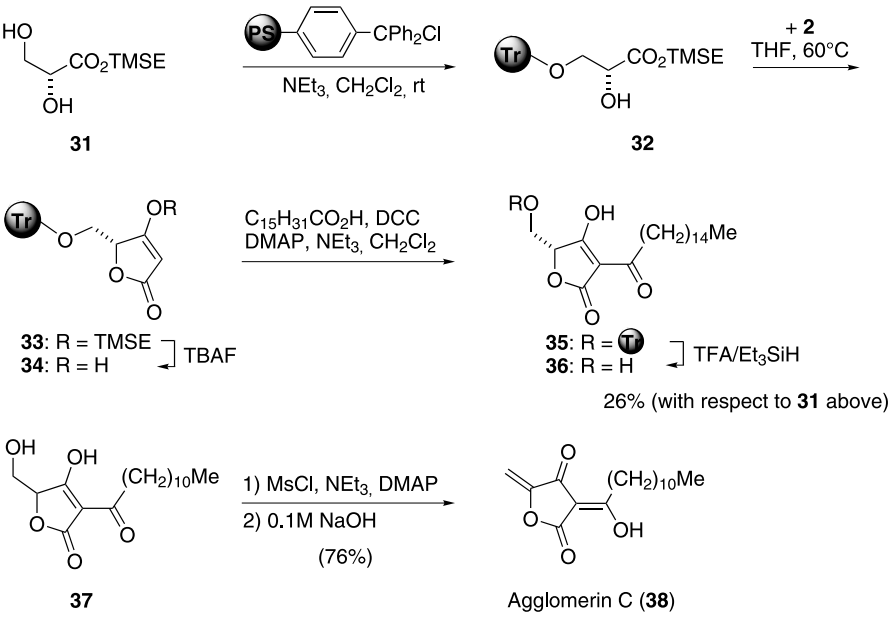
Functional groups like the β-carboxylic acid in malic acid were also used to immobilize the carbonyl precursor by mask-linking it to suitable supporting resins. This allows for the generation of libraries of tetronic acids with potential biological activity. The potent enzyme inhibitor 3-palmitoyl-5-hydroxymethyl-tetronic acid RK-682 (**36**) was prepared in this way [34]. It had originally been isolated from various strains of *Actinomycetes* and *Streptomycetes* [35] and was found to inhibit HIV-1 protease and various other protein phosphatases such as VHR (vaccinia VH-1 related phosphatase) and



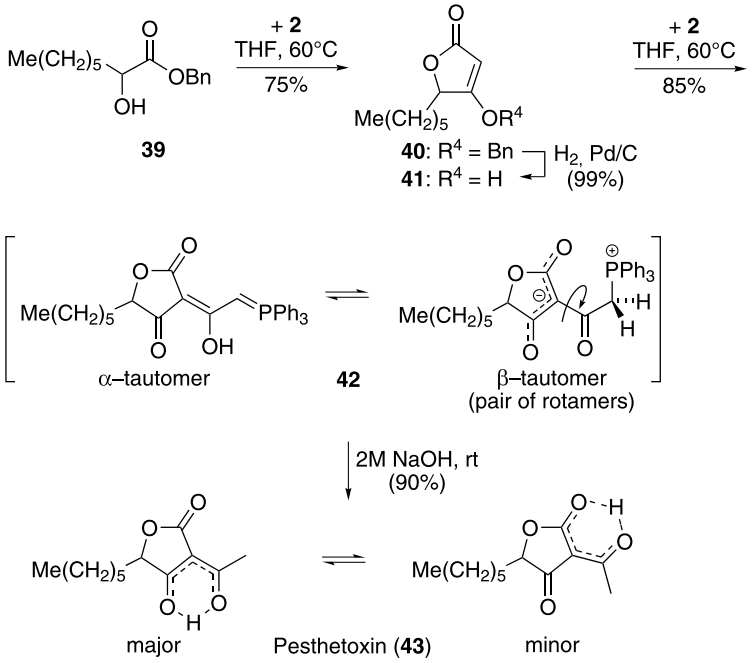
Scheme 6 Synthesis of carlosic acid 5*S*-**30** from L-malate **24** and Ph_3PCCO (**2**). Reagents and conditions: (*i*) $(CH_3CO_2)_2O$, neat, rt, 40 min; evaporation, then $PhCH_2OH$, rt, 3 h; (*ii*) CH_2Cl_2, DCC, DMAP, $Me_3Si(CH_2)_2OH$ = TMSEOH, 0 to 25 °C, 16 h, 50%; (*iii*) **2**, C_6H_6, 60 °C, 16 h; (*iv*) 5% Pd/C, H_2 (1 bar), MeOH, rt, 1 h, 99%; (*v*) DCC, DMAP, NEt_3, $C_3H_7CO_2H$, CH_2Cl_2, 0 to 25 °C, 15 h; (*vi*) TBAF · $3H_2O$, THF, rt, 2 h, 90%

cdc25B, which is a key enzyme for cell-cycle progression [36]. Structure–activity relationship (SAR) studies revealed the essential interactions between 3-acyl-5-hydroxymethyl-tetronic acids such as RK-682 and the active site in the phosphatases [37]. In a solid-phase synthesis of **36** the TMSE-ester **31** was immobilized by DMAP-catalyzed etherification of its primary OH-group with a trityl chloride tagged polystyrene resin. The resulting resin-bound ester **32** was cyclized with Ph_3PCCO (**2**) in THF instead of benzene to allow for a better swelling of the resin. The TMSE group was then selectively removed with TBAF without affecting the trityl linker. This furnished immobilized tetronic acid **34**, which is a valuable entry point for the construction of libraries of analogs of RK-682 with diversity in the 3-alkanoyl residue. With palmitic acid under Yoshii conditions, immobilized 3-acyltetronic acid **35** was obtained and eventually detached with TFA and Et_3SiH to leave **36** in 26% overall yield with respect to **31**. Antibiotic agglomerins, e.g. agglomerin C (**38**), were prepared by the same route extended by a two-step mesylation-elimination sequence (Scheme 7, bottom).

As ylide **2** also adds CH-acidic compounds, and tetronic acids are in fact CH-active β-ketoesters, 3-acetyltetronic acids can be built up by using two equivalents of **2**, one for the cyclization proper, and the other for attaching the 3-acetyl group. For example, the natural phytotoxin pesthetoxin (**43**), a leaf necrosis-inducing metabolite of the Grey Blight fungus *Pestalotiopsis theae* that regularly infects tea crops [38], was prepared as depicted in Scheme 8 [39]. The racemic 5-hexyltetronic acid **41** was readily obtained from ylide **2** and α-hydroxyoctanoic acid **39** by the usual cyclization–deprotection sequence. Acylation at C3 of **41** with another equivalent of **2** in refluxing THF afforded acyl ylide **42** as a mixture of an enol–ylide tautomer (α) and a keto–phosphonium tautomer (β). Low temperature ^{13}C and ^{31}P NMR stud-



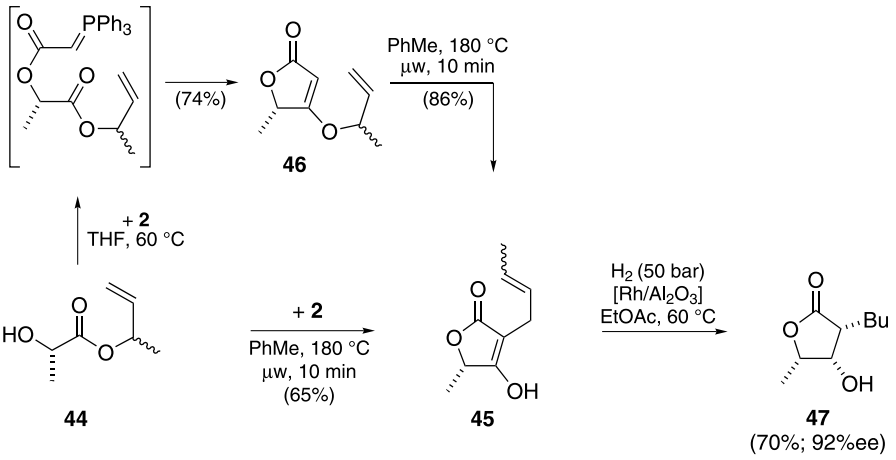
Scheme 7



Scheme 8

ies revealed that the β-tautomer actually exists as a mixture of two distinct rotamers. Acyl ylide **42** can be isolated if desired, or hydrolyzed with aqueous NaOH at room temperature to afford pesthetoxin **43**, which also exists as a mixture of two tautomers. According to NMR in the usual organic solvents, the tautomer featuring an H-chelate between the exocyclic and the 4-carbonyl groups is dominant (e.g. by 1.6 : 1 in $CDCl_3$). Either tautomer encompasses a subset of two so-called internal tautomeric forms with differently localized double bonds. However, these interconvert too quickly to be discernable in the NMR, even at temperatures as low as –60 C.

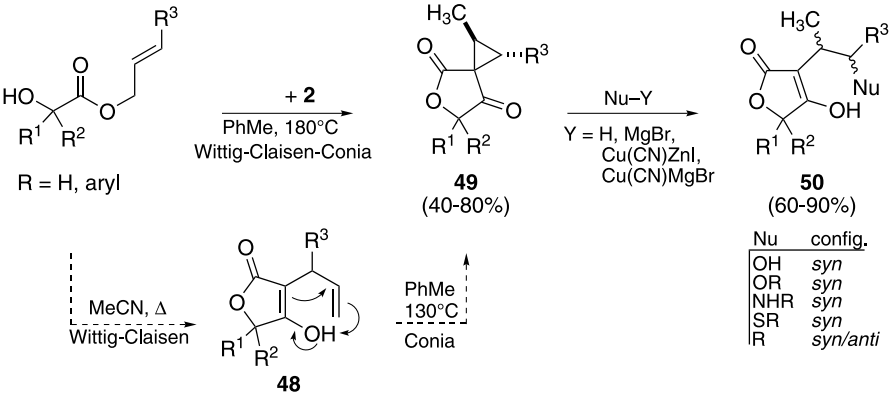
The direct synthesis of 3-alkyltetronic acids from α-hydroxy acid derivatives and ylide **2** was also accomplished by another route. When allyl esters of α-hydroxy acids are reacted with ylide **2**, further pericyclic reactions may ensue after the cyclization step, depending on the temperature and solvent polarity [40]. For example, a one-pot reaction of α-methallyl (*S*)-lactate (**44**) and **2** in toluene under microwave irradiation afforded the 5-methyl-3-but-2′-enyltetronic acid **45** in 65% yield. The reaction could also be carried out stepwise by first preparing the methallyl tetronate **46** in THF and then performing a Claisen rearrangement in a microwave oven. Simultaneous hydrogenation of both olefinic double bonds at 50 bar on a Rh/Al_2O_3 catalyst (20 mol %) afforded the natural γ-lactone (–)-3-*epi*-blastmycinolactol (**47**) with 92% ee (Scheme 9) [39].



Scheme 9

Under forcing conditions, 4-*O*-allyl tetronates rearrange to the corresponding 3-spirocyclopropylfuran-2,4-diones (**49**), by a sequence comprised of a Claisen rearrangement, to give the respective 3-allyltetronic acids **48** and a Conia oxa-ene reaction of the latter [40, 41]. When performed in gently refluxing acetonitrile the reaction yields only Claisen products **48**. The spiro-

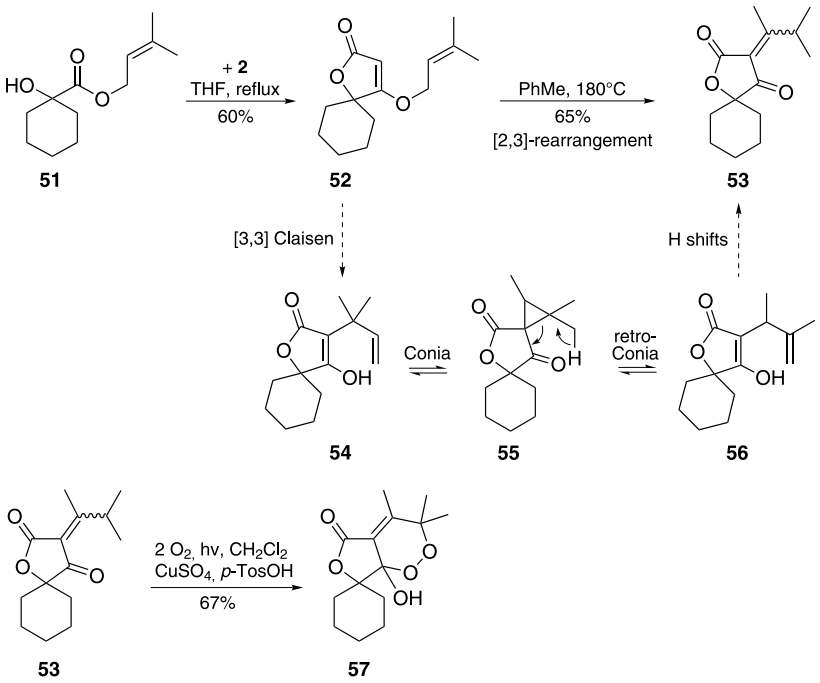
lactones **49** are generally obtained as 1 : 1 mixtures of racemic diastereoisomers that can easily be separated by crystallization. These reactions proved quite useful. A wide range of carbon and heteroatom nucleophiles can open the three-membered ring in such a way as to produce selectively either *syn*- or *anti*-1′,2′-disubstituted 3-alkyltetronic acids **50** with interesting biological properties (Scheme 10) [42, 43].



Scheme 10

Allylesters of α-hydroxycarboxylic acids bearing two or three alkyl substituents on the alkene group (such as **51**) are converted directly to [2, 3]-rearranged 3-alkylidenetetronic acids (such as **53**) upon reaction with ylide **2** in toluene at 180 °C in a sealed glass tube. A plausible mechanism is outlined in Scheme 11. An initial addition–Wittig olefination process led to allyltetronate **52**, which was only isolable when the reaction was conducted in THF at a lower temperature. Compound **52** underwent a [3,3]-Claisen rearrangement to give the 3-allyltetronic acid **54**, which was not isolable either. It entered into a Conia-type oxa-ene reaction leading to the elusive spirocyclopropane **55**. This opened the three-membered ring in a retro-Conia fashion to produce the 3-allyltetronic acid **56**, which is thermodynamically more stable than the alternative ring-opening product **54**. Under the applied conditions, compound **56** rearranged to the most stable end-product **53** by two sigmatropic H shifts [42, 43]. In total, the direct conversion of hydroxyester **51** into tetronic acid **53** is actually a seven-step domino sequence. When set under an atmosphere of air or oxygen, the reaction between **51** and **2** in toluene at 180 °C afforded directly the endoperoxide **57** [44]. This compound, which exhibits an antiplasmodial activity exceeding that of the natural antimalarial artemisinin, was obtained in better yields by controlled photooxygenation of 3-alkylidene-tetronic acid **53** [45].

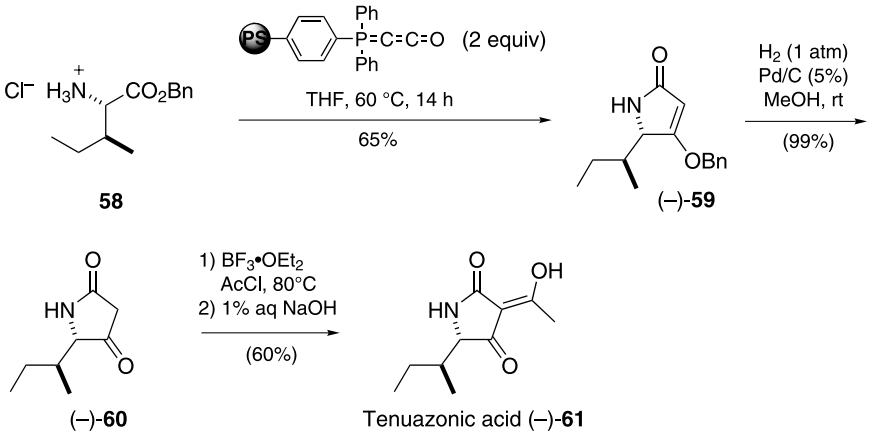
Ph_3PCCO (**2**) also adds and Wittig alkenates α-amino esters to give the corresponding tetramates, many of which are biologically active. The draw-



Scheme 11

backs of this reaction, occasional failure of *N*-substituted derivatives to react and problems with removal of by-product phosphine oxide, were overcome by using polystyrene-bound ylide **2**. Both primary and secondary α-amino esters as well as their ammonium salts react with immobilized ylide PS–**2** to give tetramates in good yields. Ammonium salts, which are the customary form of storage of α-amino esters, generally react faster than the latter. An excess of PS–**2** can be used to deprotonate/cyclize them in one pot. Scheme 12 depicts a straightforward three-step synthesis of optically pure tenuazonic acid (–)-**61**, a mycotoxin exhibiting a broad spectrum of biological activity [46, 47]. It was first isolated in 1957 from the culture filtrates of *Alternaria tenuis* and later on also from other *Alternaria* and *Pyricularia* species [48, 49]. Isoleucine benzyl ester chloride **58** was reacted with a twofold excess of ylide PS–**2** in THF at 60 °C to give tetramate (–)-**59**. Its debenzylation by hydrogenolysis quantitatively furnished 5-*S*-butylpyrrolidine-2,4-dione (5*S*,6*S*)-**60**. Acylation of the latter by the protocol of Jones [50] with an excess of acetyl chloride and boron trifluoride–diethyl etherate and hydrolytic work-up gave tenuazonic acid (–)-**61** as a mixture of various tautomers in 60% yield [15].

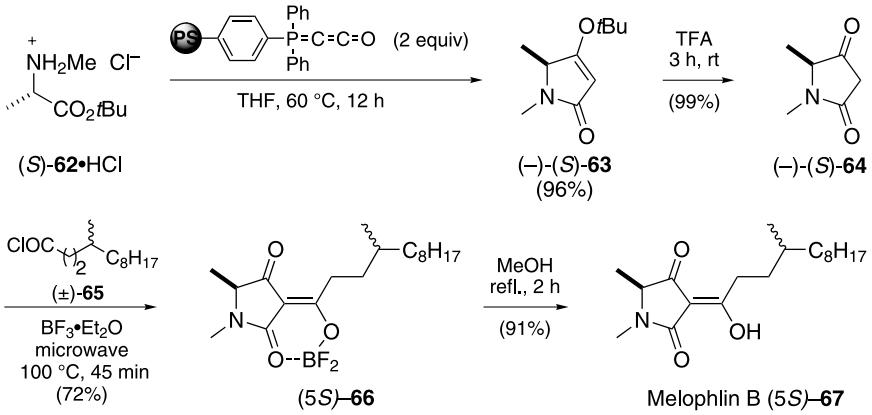
Pharmacologically more interesting than tenuazonic acid are the melophlins, a class of *N*-methyl-3-acyltetramic acids recently isolated from the marine sponge *Melophlus sarassinorum*. Melophlins A and B displayed cy-



Scheme 12

totoxic activity against HL60 cells and also arrested NIH3T3 cells in the G_1 phase of the cell cycle, while melophlins C and G were active against *B. subtilis* and *S. aureus*, the brine shrimp *Artemia salina* and the larvae of the pest insect *Spodoptera littoralis*. Melophlin C was also found active against *Candida albicans* [51]. The 5-unsubstituted melophlins A and G were prepared in just four steps from sarcosine *t*-butyl ester. The absolute configuration at C-5 of melophlin B (**67**) was shown to be *S* by oxidative degradation to *S*-alanine, while the side-chain is racemic at the methyl-substituted carbon atom C-4′. (5*S*)-**67** was prepared from commercially available (*S*)-*N*-methylalanine *t*-butyl ester hydrochloride (*S*)-**62**HCl (Scheme 13) [52].

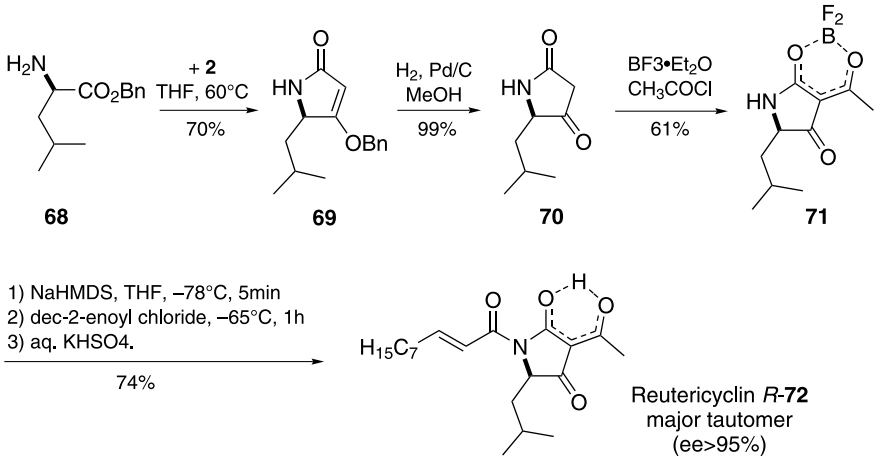
Treatment of this salt with two equivalents of immobilized ylide PS–**2** furnished *t*-butyl tetramate (–)-(*S*)-**63** in 96% chemical yield and 99% ee.



Scheme 13

Quantitative cleavage of the ester with TFA gave 1,5-dimethylpyrrolidine-2,4-dione (–)-(*S*)-**64**. This was 3-acylated according to Jones's protocol with 4-methyldodecanoyl chloride (±)-**65** to give the corresponding BF_2-adduct **66** in a moderate 40% yield under classical thermal conditions, but in 72% yield under microwave irradiation conditions. **66** was finally converted to melophlin B (5*S*)-**67** by boiling in methanol.

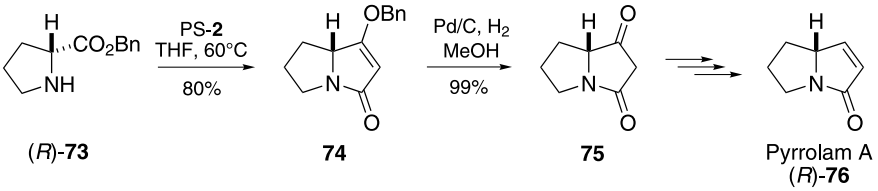
The 1,3-bisacylsubstituted tetramic acid reutericyclin *R*-**72**, which was first obtained from a sourdough isolate of *Lactobacillus reuteri* by Jung et al. [53, 54], exhibits antibiotic activity against a wide variety of Gram-positive bacteria. The Jung group published two syntheses of **72**, which differed in the procedure of the ring closure and in the order of introduction of the acyl residues at N-1 and C-3 [55, 56]. Both proceeded with at least partial racemization. Our group developed an alternative four-step synthesis of *R*-**72** from D-leucine benzyl ester **68**, which was cyclized with ylide **2** in solution, as separation of the product tetramate **69** from phosphine oxide was not a problem here. The corresponding tetramic acid **70** was then submitted to two non-racemizing acylations, first at C-3 under Jones' conditions with acetyl chloride/BF_3 etherate, then at N-1 using NaHMDS/decenoyl chloride at low temperature (Scheme 14). The BF_2-chelated complex **71** was stable towards bases, acting as a built-in protecting group for the acetyl residue in the subsequent deprotonation/acylation at N-1. Treatment of **71** with sodium disilazanide (NaHMDS) for 5 min at –78 °C in THF solution, followed by immediate quenching with *E*-dec-2-enoyl chloride and final aqueous work-up produced an enantiomerically pure sample of reutericyclin **72** (ee > 95%) [39].



Scheme 14

Pyrrolizidinones are likewise accessible from prolinates. (–)-(*R*)-Pyrrolam A (**76**), which was isolated by Zeeck et al. [57] from *Streptomyces olivaceus*

(strain Tü 3082) was prepared in five steps, 95% ee and 25% yield from benzyl prolinate (*R*)-**73** and ylide **2** immobilized on a polystyrene resin (Scheme 15) [58]. An indolizidinone was obtained analogously from benzyl pipecolate.

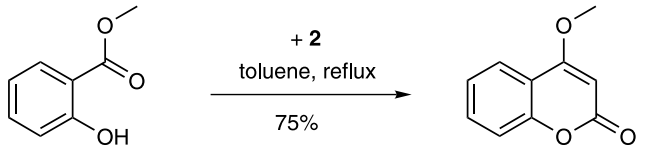


Scheme 15

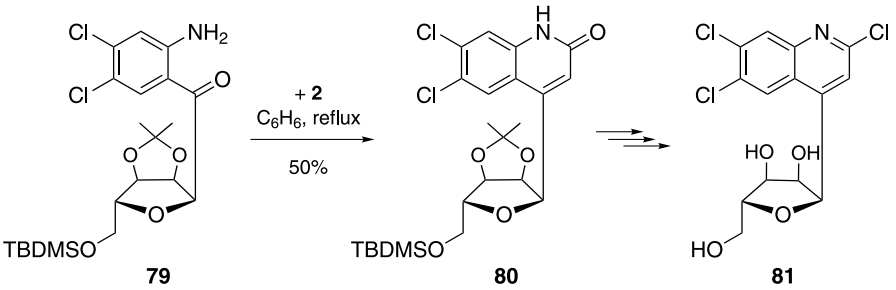
2.4 Other Heterocycles

Six-membered heterocycles were obtained early on from **2** and β-functionalized esters [4]. Salicylates **77**, anthranilates and thiosalicylates gave rise to coumarins **78** (Scheme 16), quinolones and thiocoumarins, respectively.

α-(Hydroxylimino)esters reacted with **2** to give 1,2-oxazine-6-ones [59]. The general method was also applicable to the synthesis of seven-membered systems such as benzoxepinones and azepinones from *o*-hydroxy- or *o*-amino-



Scheme 16



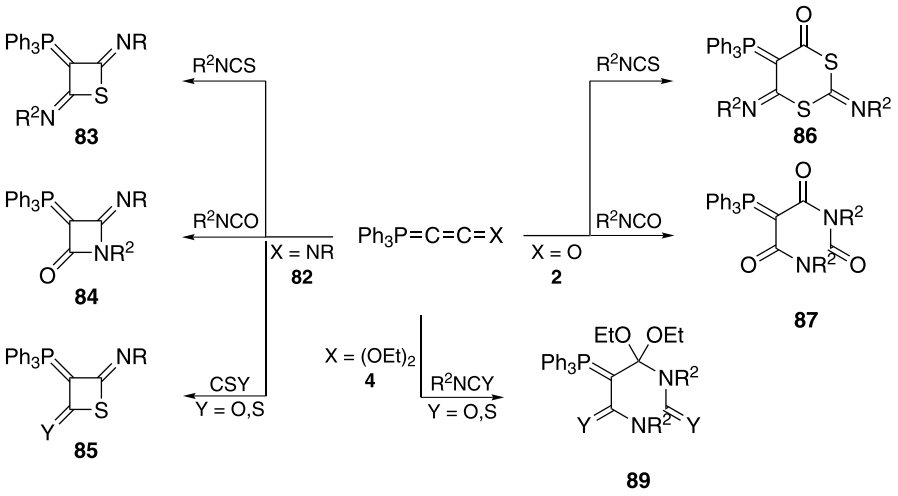
Scheme 17

phenyl acetates [30]. More recently, Townsend et al. [60] prepared antiviral polyhalogenated quinoline C-nucleosides such as 4-(*R*-D-ribofuranosyl)-2,6,7-trichloroquinoline **81** with activity against human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1). The key step was the cyclization of *o*-acylaniline **79** with ylide **2** to give quinolone **80** in 50% yield (Scheme 17).

3
Heterocycles from Non-Wittig Reactions

3.1
Cycloaddition Reactions

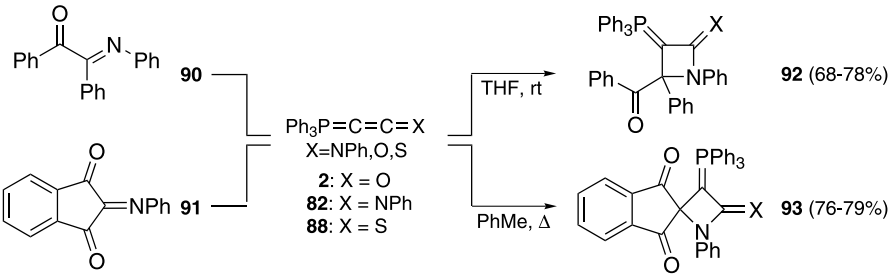
Cumulated ylides $Ph_3P{=}C{=}C{=}X$ have been reported to form heterocycles by [2 + 2]- and [2 + 4]-cycloaddition reactions with other multiple-bond systems such as ketenimines, isocyanates, isothiocyanates, CO_2, COS, CS_2 etc. [11]. Depending on the respective combination and stoichiometry, addition occurs either to the P–C^{α} or to the C^{α}–C^{β} bond of the starting ylide to give various types of four- and six-membered heterocycles (Scheme 18). Addition onto the C^{α}–C^{β} bond normally takes place in such a way that the most nucleophilic atom of the non-ylidic component becomes bound to C^{β}. For example, triphenylphosphoranylideneketen-imines, $Ph_3P{=}C{=}C{=}NR$ (**82**), yield thietanes **83** and **85** upon reaction with CS_2 [61], COS and isothiocyanates, whereas azetidinones **84** are formed with isocyanates due to sulfur being more strongly nucleophilic than oxygen or nitrogen [11]. The cyclic prod-



Scheme 18

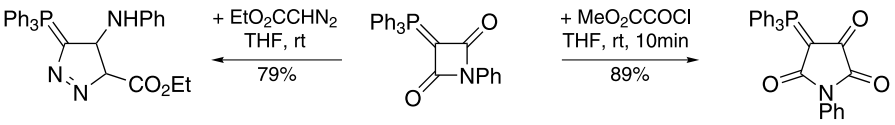
uct ylides **83–85** can be Wittig alkenated with aldehydes. While four-ring formation is typical of ylides **82**, ylide **2** furnishes six-membered heterocycles **86** and **87** with isocyanates and isothiocyanates [62]. Interestingly, reaction of **2** with CS_2 gives rise to triphenylphosphoranylidenethio-ketene, $Ph_3P{=}C{=}C{=}S$ (**88**), by spontaneous loss of COS in the intermediate thietane [63]. Unlike ylide **2**, diethoxyvinylidenetriphenylphosphorane (**4**) affords pyrimidines **89** when reacted with isocyanates or isothiocyanates [64]. Ylide **88** is so unreactive that it undergoes [2 + 2]-cycloaddition reactions only with very reactive aryl isocyanates and isothiocyanates to give the corresponding azetidinones and thietanes, respectively [65, 66].

Lately, Soliman et al. [67] replaced isocyanates in the above reactions by the monoanils of benzil (**90**), *o*-naphthoquinone or triketones (such as **91**) only to obtain the corresponding azetidinones (**92, 93**) with each of ylides **2**, **82** or **88** (Scheme 19). However, reactions were not run at 2 : 1 (imine : ylide) stoichiometry.



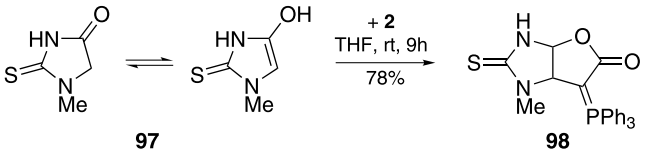
Scheme 19

Follow-up chemistry of azetidyl ylide **94**, which was obtained by hydrolysis of ylide **84**, led to various pyrrolidines and pyrazoles [68]. The reaction with methyl oxalyl chloride gave a 4-triphenylphosphoranylidene-pyrrolidine-2,3,5-trione **95**, while treatment with ethyl diazoacetate afforded 4-anilido-3-triphenylphosphoran-ylidene-pyrazole-5-carboxylic acid ethyl ester **96** (Scheme 20).



Scheme 20

A formal [2 + 3] cycloaddition reaction between ylide **2** and thiohydantoin **97** affording furo[2,3-*d*]imidazol-5-one **98** was found by Boulos et al. [69].

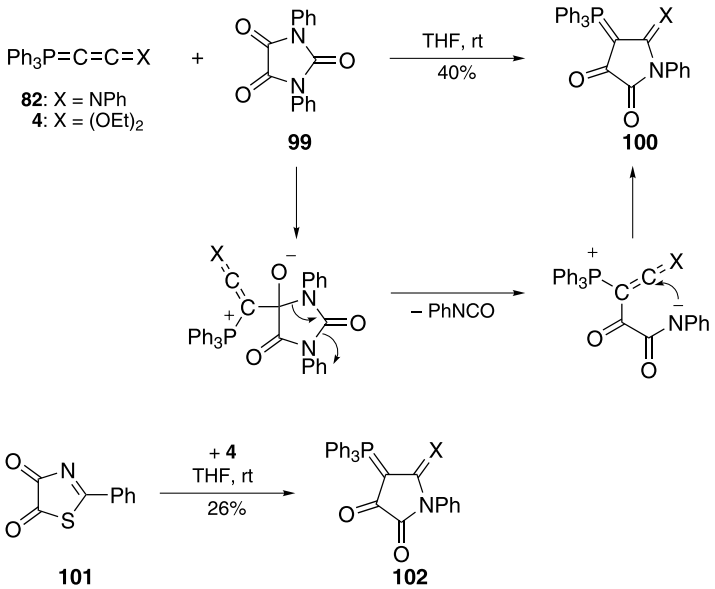


Scheme 21

The connectivity of the enamine and ylide moieties is unusual and remarkable (Scheme 21).

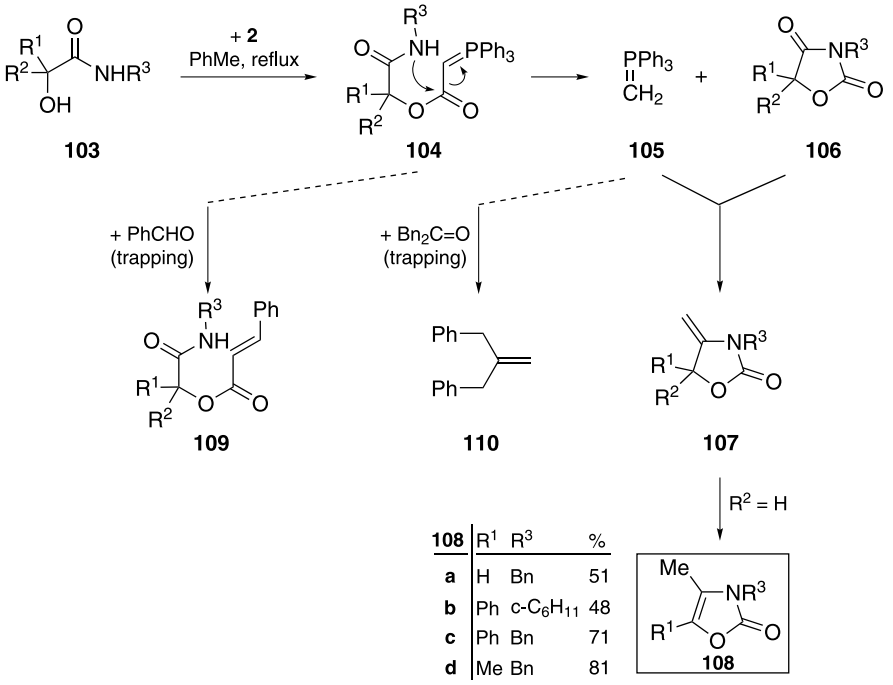
3.2 Other Methods

Imino derivatives **100** of compounds of type **95** were also directly prepared from cumulated ylides **82** or **4** and parabanic acid derivatives **99** by a presumed mechanism as depicted in Scheme 22 [70]. Attack of the nucleophilic ylidic carbon atom at the most electrophilic amide-type carbonyl carbon atom, ring opening with loss of phenyl isocyanate, and recyclization by N–C bond formation are the key steps. This reaction is reminiscent of an older one, furnishing 5,5-diethoxy-1-thiobenzoyl-4-triphenylphosphoranylidene-pyrrolidine-2,3-dione **102** from 2-phenylthiazoline-4,5-dione **101** and **4** [71] in modest yield.



Scheme 22

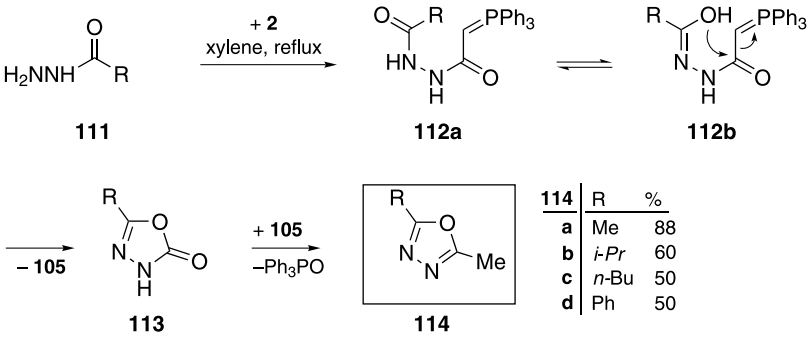
An unusual cascade implying three different ylide species, none of which closes the ring via Wittig olefination, was found for α-hydroxy amides **103** [59]. Their reaction with **2** did not yield 4-amino-substituted butenolides by the usual addition–Wittig olefination process but 4-methyl-2-[3H]-oxazolones **108** instead. With amides **103** bearing tertiary hydroxy groups, mixtures of 4-methylene-2-oxazolidinones **107** (65%) and 2,4-oxazolidinediones **106** (25%) were isolated in cases where the residues were relatively small (R^1, R^2 = Me, R^3 = Bn). Amides **103** featuring bulkier residues like R^1, R^2 = Ph, R^3 = Bn gave exclusively the corresponding dioxo compounds **106** (60%) (Scheme 23). Mechanistically, the OH-function of hydroxy amide **103** adds across the C=C bond of **2** to give the acyl ylide **104**, which then cyclizes by a nucleophilic attack of the nitrogen atom at the ylidic carbonyl carbon atom to give **106** with concomitant expulsion of methylenetriphenylphosphorane **105**. By an intermolecular Wittig reaction, **105** then olefinates the amide-type carbonyl function of **106** to afford the 4-methylene compound **107**, which in turn normally tautomerizes to yield the product heterocycles **108**. Only amides **103** lacking α-protons furnish unrearranged 4-methylene-2-oxazolidinones **107**. This cascade is unusual and somewhat "up-hill" in character as it implies three different types of phosphorus ylide of increasing "Wittig-reactivity", which could all be trapped. When benzal-



Scheme 23

dehyde was added to the reaction mixture prior to heating, cinnamoate **109** was isolated in nearly quantitative yield as the product of an intermolecular Wittig olefination with the stabilized ylide **104**. When a mixture of **103**, **2** and diphenylacetone was heated, the reaction proceeded up to the extrusion of **105**, which then olefinated diphenylacetone to give dibenzylethene **110** alongside 2,4-oxazolinedione **106** in almost equal yields. The latter are of considerable interest because of their analgesic, hypnotic and anticonvulsant activities.

Hydrazides **111** reacted similarly with ylide **2** and yielded 5-methyl-1,3,4-oxadiazoles **114** (Scheme 24) [72]. Addition of the amino group to the ylide **2** produced an amide ylide **112a** that did not undergo an intramolecular Wittig olefination but tautomerized to the hydroxy compound **112b** instead. This in turn cyclized to **113** by nucleophilic attack of the oxygen atom on the ylidic carbonyl carbon atom with concomitant extrusion of **105**. Ylide **105** then intermolecularly olefinated the carbonyl group of **113** to give the elusive 5-methylene-1,3,4-oxadiazolines that quickly tautomerized yielding the end product **114**. N-substituted hydrazides were found unreactive.

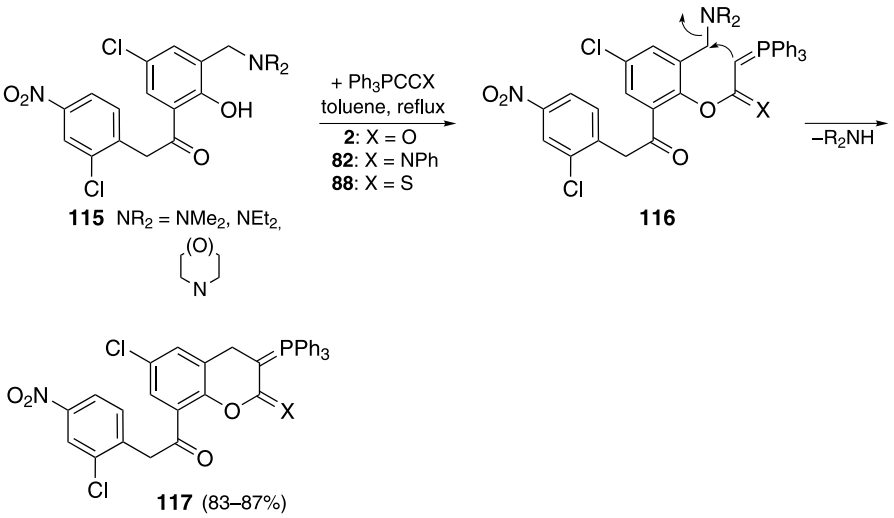


114	R	%
a	Me	88
b	*i-Pr*	60
c	*n*-Bu	50
d	Ph	50

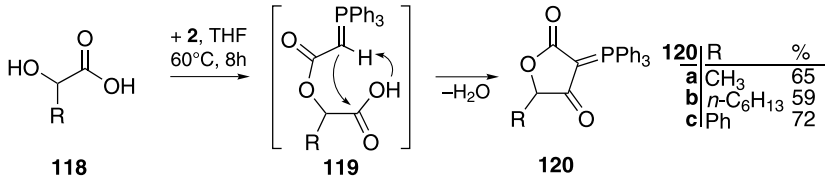
Scheme 24

Soliman et al. reported the synthesis of 3-triphenylphosphoranylidene-chromanes **117** from Mannich bases **115** of the commercial molluscicide niclosamide and the cumulated ylides **2**, **82** or **88** [73]. The reaction was carried out in boiling toluene and is thought to proceed by initial addition to give the acyl ylides **116**, which then cyclize by the unusual expulsion of a secondary amine, i.e. by nucleophilic attack of the ylidic carbon atom at the benzylic carbon atom. Intermediates **116** were not isolated. The molluscicidal activities of compounds **117** were found to be about tenfold lower than that of the parent niclosamide (Scheme 25).

3-Triphenylphosphoranylidene dihydrofuran-2,4-diones **120** are accessible from α-hydroxycarboxylic acids **118** and ylide **2** in good yields and without racemization [39]. For instance, (+)-**120c** was obtained in 95% ee from L-(+)-mandelic acid (Scheme 26). In contrast to the reaction of α-hydroxy-



Scheme 25

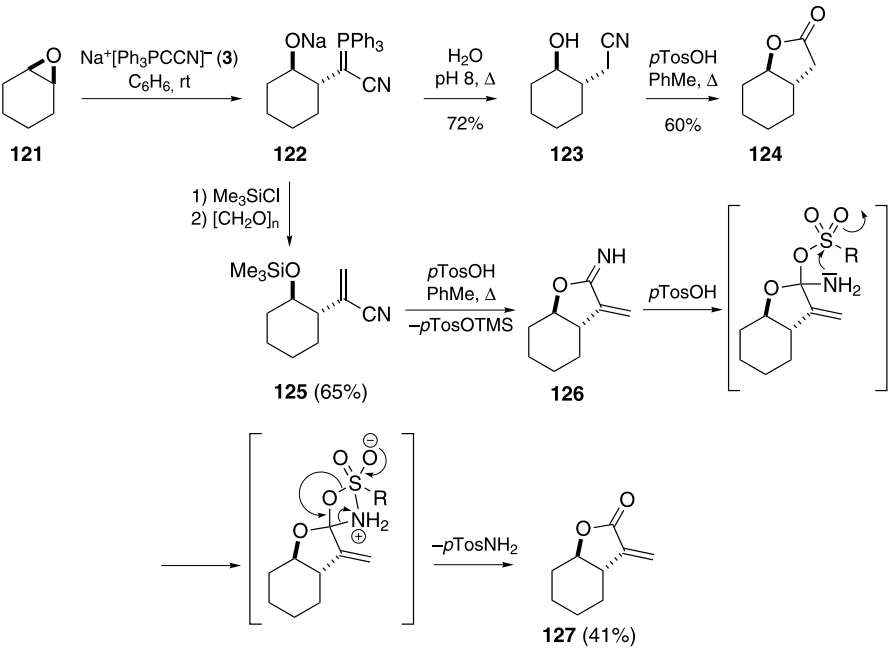


Scheme 26

esters with **2** (see Schemes 5 and 7), the intermediate acyl ylide **119** eliminates water rather than undergoing an intramolecular Wittig alkenation. Amazingly, even aqueous solutions of lactic acid reacted with the water-sensitive ylide **2** to afford **120a**, if some drying agent was added to the mixture in refluxing THF.

4
Heterocycles from Ylide Anions and Vinyl Phosphonium Salts

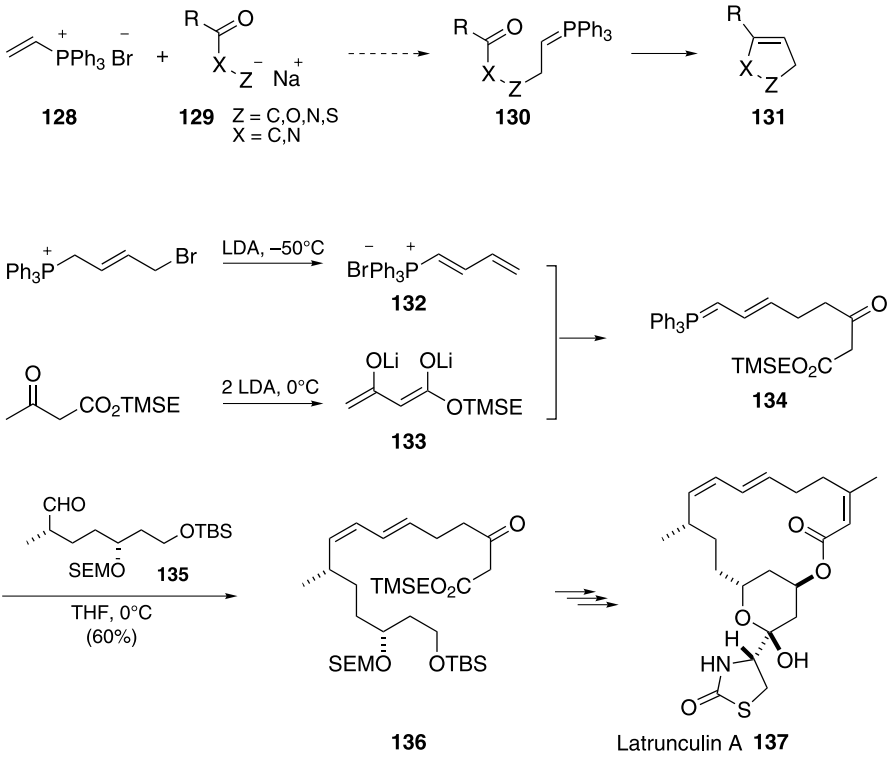
The highly nucleophilic ylide anion of sodium [cyano(triphenylphosphoranylidene)methanide] **3**, which is available by deprotonation of cyanomethylene triphenylphosphorane with sodium silazanide in benzene solution at room temperature [74], attacks oxiranes by ring-opening. Depending on the work-up conditions and the further reactions employed, γ-hydroxynitriles, γ-butyrolactones or α-methyleno-γ-butyrolactones were obtained from the primary products thus formed (Scheme 27) [16]. For in-



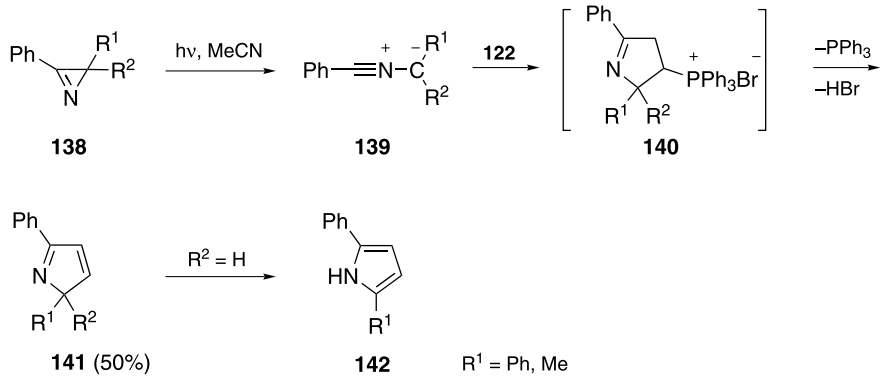
Scheme 27

stance, cyclohexene oxide **121** was ring-opened by **3** to give the cyanoylidated sodium alkoxide **122**. Hydrolysis of the latter led to γ-hydroxynitrile **123**, which in turn was cyclized upon refluxing with one equivalent of *p*TosOH in toluene to afford the γ-lactone **124**. O-silylation of the alkoxide **122** and subsequent Wittig alkenation of the so-formed β-silyloxy-cyanoylide with paraformaldehyde furnished the corresponding vinylnitrile **125**. The latter, when heated in toluene with two equivalents of *p*TosOH, afforded α-methyleno-γ-butyrolactone **127**. In this case one equivalent of *p*TosOH was spent to form the intermediate imidolactone **126**.

Vinyltriphenylphosphonium salts **128** were introduced by Schweizer et al. as early as 1964 for preparation of various types of heterocycles including dihydrofurans [75], pyrrolizidines [76] and 1,2-dihydroquinolines [77] from different nucleophilic ω-carbonylated anions **129**. The latter, customarily prepared in situ, add to the vinyl group to generate a reactive ω-carbonylylide **130**, which then undergoes an intramolecular Wittig alkenation reaction to **131**. This method even worked well for δ-carbonylylides of the amide type (**130**: X = NR, Z = C here) in which case pyrrole derivatives were formed (Scheme 28, top). Enolates were also used as C-nucleophiles in similar reactions with butadienyltriphenylphosphonium bromide **132**. An interesting application of this variant was part of the synthesis by White and Kawasaki [78] of the ichthyotoxin (+)-latrunculin A **137**, originally isolated from the Red



Scheme 28



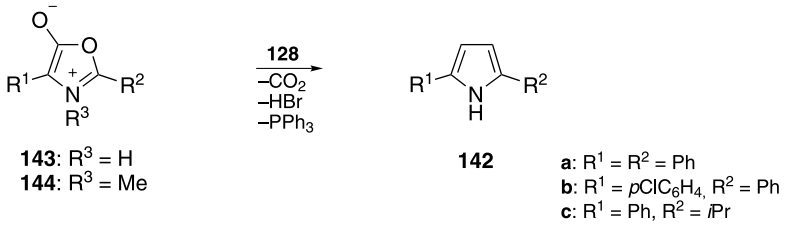
Scheme 29

Sea sponge *Latrunculla magnifica* (Keller). For elaboration of its C(1)–C(15) segment, bromide **132** (prepared by treatment of the corresponding allylphosphonium bromide with strong base) was reacted at low temperature with a solution of the dilithio dianion **133**, prepared from 2-(trimethylsilyl)ethyl

acetoacetate. The resulting cold red solution of vinyl ylide **134** was then treated with aldehyde **135** to furnish (*E*, *Z*)-**136** as the sole diene isomer. If warmed up in the absence of an aldehyde, ylide **134** would have undergone self-olefination.

On irradiation in acetonitrile, 3-phenyl-2*H*-azirines of type **138** react with triphenylvinylphosphonium bromide **128** to form 2*H*-pyrroles **141** (Scheme 29), presumably via the photochemically generated dipoles **139** and the products **140** of a [2+3]-cycloaddition reaction between **138** and **139** [79]. Derivatives of **141** bearing an α-H rearrange to the pyrroles **142**.

In a more recent variant by Gelmi et al. [80], 5(4*H*)-oxazolones **143** and münchnones **144** were used as sources for 1,3-dipoles in thermal cycloaddition reactions with phosphonium salt **128**. 3-Methylpyrroles and 3-pyrrole carboxylic acids were obtained likewise from substituted vinylphosphonium salts. The cycloaddition reactions proceed with high regioselectivity (Scheme 30).



Scheme 30

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Author Index Volumes 1–12

The volume numbers are printed in italics

Subject Index