Topics in Current Chemistry

Jianbo Wang Editor

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Aims and Scope

The series Topics in Current Chemistry presents critical reviews of the present and future trends in modern chemical research. The scope of coverage includes all areas of chemical science including the interfaces with related disciplines such as biology, medicine and materials science.

The goal of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights are emerging that are of interest to larger scientific audience.

Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5 to 10 years should be presented. A description of the laboratory procedures involved is often useful to the reader. The coverage should not be exhaustive in data, but should rather be conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

Readership: research chemists at universities or in industry, graduate students.

Jianbo Wang
Editor

Stereoselective Alkene Synthesis

With contributions by

I. Chataigner · Y. Gu · S. Hara · Y. Hu · X. Lei · H. Li · J. Maddaluno · K. Matsumoto · M. De Paolis · M. Shindo · W.-Y. Siau · S.-K. Tian · J. Wang · Y. Zhang · Y. Zhang · X.P. Zhang · Y. Zhao

Springer

Editor
Jianbo Wang
Peking University
Beijing
China

ISSN 0340-1022 ISSN 1436-5049 (electronic)
ISBN 978-3-642-31823-8 ISBN 978-3-642-31824-5 (eBook)
DOI 10.1007/978-3-642-31824-5
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2012943861

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

The stereoselective synthesis of olefins has been one of the major topics in the arena of organic synthesis for many decades. The methods for olefin synthesis have evolved from classic elimination reactions to more modern methods such as the Wittig reaction and its variants, cross-coupling reactions and olefin metathesis. Numerous reviews are available on these topics. The purpose of this special volume is to cover the most recent advances in this ever-growing field, with a focus on stereocontrol in C=C double formation.

Two chapters in this volume highlight the recent development of the widely used methods for olefin synthesis, namely Wittig reactions (Chapter 7) and olefin metathesis (Chapter 6). For olefin metathesis, the focus is put on its applications in complex natural product synthesis. Owing to the importance of introducing fluorine atoms to organic molecules, the methods for the stereoselective synthesis of monofluoroalkenes have been summarized in Chapter 3. 1,3-Dienes, as a special type of olefin, widely exist in natural products, and also find various applications in organic synthesis. Therefore, stereoselective synthesis of 1,3-dienes is considered as an important part of olefin synthesis. This is also included in this special volume (Chapter 4).

Stereoselective synthesis of tetrasubstituted alkenes remains a challenging task. A unique solution to this problem is to use torquoselectivity-controlled olefination of carbonyl compounds with ynolates, which is summarized in Chapter 1. In general, the stereoselective synthesis of *Z*-alkenes, which are thermodynamically less favorable, is more difficult than the synthesis of corresponding *E*-isomers. In Chapter 2, various methods for stereoselective synthesis of *Z*-alkenes are reviewed. Finally, the C=C double bond formation through catalytic carbene transformation has recently emerged as a new approach toward olefin synthesis. Two chapters covering olefin synthesis based on catalytic carbene transformations are included (Chapter 5 and Chapter 8) .

Having read all the chapters, I hope that readers are left with the notion that stereoselective olefin synthesis is still a rapidly growing area with constant emergence of novel synthetic methods.

I would like to thank Prof. Henry N. C. Wong for his encouragement and support, Karin Bartsch and Elizabeth Hawkins for their assistance in the whole process. I would also like to thank the referees for their invaluable comments and suggestions. Finally, this book would not have been possible without the participation of the authors, to whom I am deeply indebted for their enduring patience throughout this project.

Beijing, June 8, 2012 Jianbo Wang

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Top Curr Chem (2012) 327: 1–32
DOI: 10.1007/128_2012_313

Published online: 6 March 2012

Stereoselective Synthesis of Tetrasubstituted Alkenes via Torquoselectivity-Controlled Olefination of Carbonyl Compounds with Ynolates

Mitsuru Shindo and Kenji Matsumoto

Abstract The efficient synthesis of tetrasubstituted alkenes by the olefination of carbonyl compounds with ynolates is described. This reaction involves the cycloaddition of ynolates with carbonyl groups, followed by electrocyclic ring-opening of the resulting β-lactone enolates. Orbital symmetry during the electrocyclic ring opening requires conrotatory motion. The direction of this rotation (inward or outward) determines the *E*/*Z* geometry to the tetrasubstituted olefin product through torquoselectivity. Theoretical calculations revealed that several secondary orbital interactions are essential for the high torquoselectivity. This methodology is a novel olefination for constructing multisubstituted olefins.

Keywords Electrocyclic reaction · Olefination · Secondary orbital interaction · Torquoselectivity · Ynolate

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1 Introduction

Stereoselective olefination of carbonyl groups giving tetrasubstituted alkenes is a hot topic in synthetic organic chemistry, because there have been very few reports on this process [1, 2]. These moieties are sometimes contained in natural products, such as materials of the *Stemona* alkaloids [3] and kainoid amino acids [4], drugs such as tamoxifen [5], and dipeptide mimetics (Fig. 1) [6, 7]. Importantly, tetrasubstituted olefins also contribute extensively to material sciences in such capacities as photoswitches based on photochromism [8]. Besides being useful final products, stereodefined tetrasubstituted olefins would be potential precursors for various asymmetric transformations generating contiguous stereogenic centers such as hydrogenations [9], dihydroxylations [10, 11], epoxidations [12, 13], conjugate additions [14, 15], and Heck reaction [16]. Even with the significance of these olefins, conventional direct olefination methods such as the Wittig and

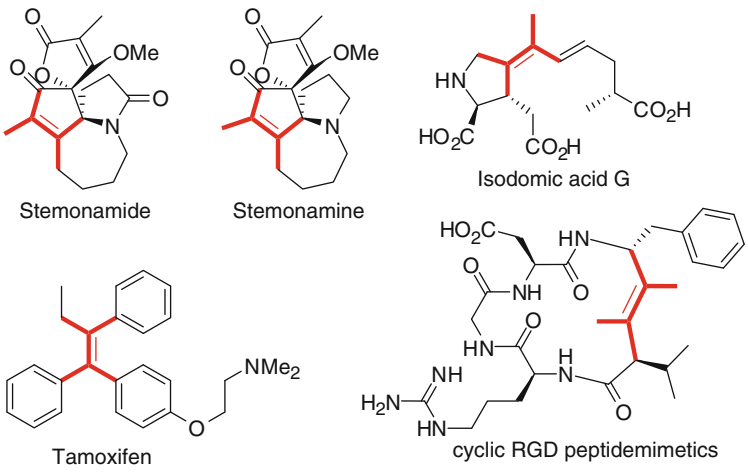


Fig. 1 Biologically active compounds with tetrasubstituted olefins

Horner–Wadsworth–Emmons reactions encounter serious problems of reactivity, stereoselectivity, and generality when used to form tetrasubstituted olefins. Most studies on the synthesis of tetrasubstituted olefins exploit alternative routes based on carbometalation of alkynes [17–19]. However, these processes have difficulties associated with the regioselectivity of the initial carbometalation and with reactivity during the final coupling. Here we describe stereoselective syntheses of tetrasubstituted olefins, via the olefination of carbonyl compounds with ynolates, as well as some synthetic applications [20, 21].

2 Preparation of Ynolates

Ynolates are carbanions having a C–C triple bond in place of a double bond that is found in enolates. Ynolates can be used as precursors of alkynyl ethers, and also ketene anions acting as ketene precursors (Fig. 2). Their chemistry would show interesting facets that are impossible to attain with enolates, and also contribute to ketene chemistry. However, ynolates have attracted little attention in synthetic organic chemistry, with only scattered reports in the literature until recently [22, 23]. Schöllkopf reported the first synthesis of an ynolate, which was generated by fragmentation of isoxazolyllithium (**2**), prepared by lithiation of 3,4-diphenylisoxazole (**1**) (Fig. 3) [24, 25]. Lithiation of trimethylsilylketene **3** with butyllithium at −100 °C provides an ynolate in good yield [26, 27]. Kowalski reported that ynolates are synthesized by the rearrangement of α-keto dianions **5**, which are prepared by adding dibromomethyllithium (**4**) to esters followed by base-induced elimination [28–30]. The hypervalent organoiodine **7** reacts with the terminal alkynes **6** to give the iodonium tosylates **8**, which are then treated with CuOTf to afford the ynol tosylates **9**. The ynol tosylates **9** are converted into ynolates by treatment with methyllithium [31, 32]. Lithium acetylides **10** are oxygenated by lithium *tert*-butylperoxide, prepared from anhydrous *tert*-butylhydroperoxide and LHMDS, to afford ynolates [33, 34]. The α-chloro-α-sulfinyl ketone **11** is dimetalated by potassium hydride and *tert*-butyllithium to give the keto dianion, which is converted into ynolate [35–38]. The trimethylsilyl ynolate **12** is prepared on treatment of trimethylsilyldiazomethane with butyllithium followed by exposure to carbon monoxide [39, 40]. Transmetalation of bis(trimethylsilyl)ketene **13** by *t*-BuOK in the presence of HMPA affords the ynolate [41].

Ynolates cannot be prepared in a similar fashion to metal enolates, because the intermediates may be labile monosubstituted ketenes. Several preparative methods for ynolates have been reported, among which some have been used as a precursor of silyl ynol ethers, that is, silyl ynolates, in organic syntheses [42–45]. However, a general methodology for the preparation of ynolates has not yet been established. This is one of the reasons why ynolates have attracted much less attention than the corresponding enolates.

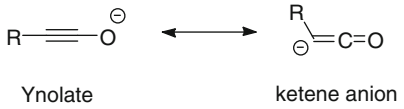


Fig. 2 Ynolates

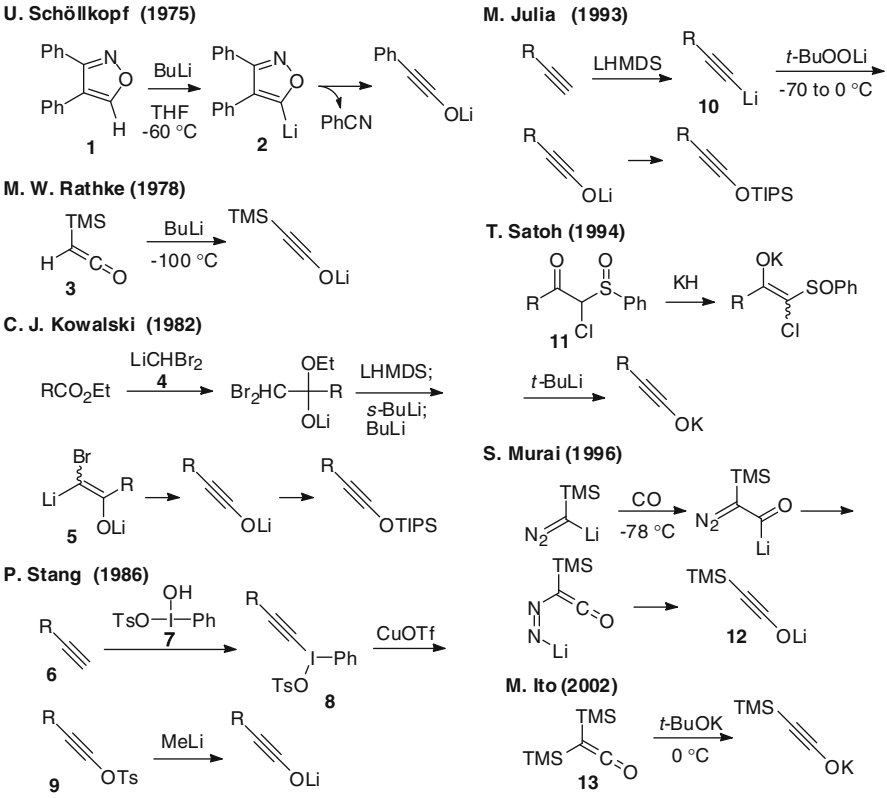


Fig. 3 Preparation of ynolates (Schöllkopf, Rathke, Kowalski, Julia, Murai, etc.)

We have developed a convenient method for the preparation of ynolates via thermal cleavage of ester dianions [46]. The starting materials are α,α-dibromo esters, which are readily prepared by bromination of bromo esters or precursors [47]. For example, 2,2-dibromopropionate **15** is synthesized by dibromination of the acyl bromide **14** via the Hell–Volhardt–Zelinski reaction (Fig. 4). In the case of 2,2-dibromocaproate **16**, the bromination with dibromotetrafluoroethane or dibromotetrachloroethane of the derived α-bromoester enolate can be employed. A THF solution of α,α-dibromo esters **17** is treated with 4 equiv. of *tert*-butyllithium or *sec*-butyllithium at –78 °C and, after 10 min, the reaction is allowed to warm to 0 °C to afford the lithium ynolate **19** solution within 30 min (Fig. 5) [48]. The efficiency of this method is estimated by the result of several reactions to be more than 90%. The butyllithium is transformed by lithium–halogen exchange into bromobutane, which is immediately decomposed by another 1 equiv. of butyllithium. Overall, 4 equiv. of butyllithium are required. The key mechanism is thermal cleavage of ester dianions **18**, prepared by double lithium–halogen exchange of **17**. This method takes advantage of the properties of ester enolates **20**, which are easily converted into ketenes **21** by the elimination of alkoxide (Fig. 6) [49, 50].

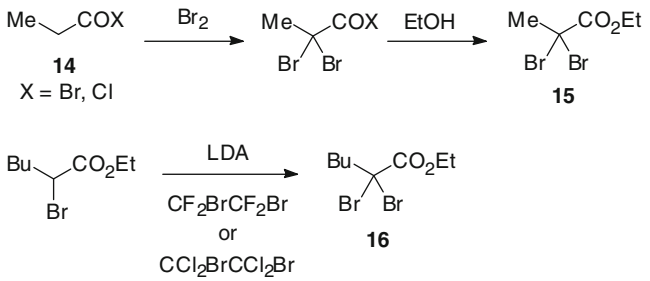


Fig. 4 Preparation of α,α-dibromo esters

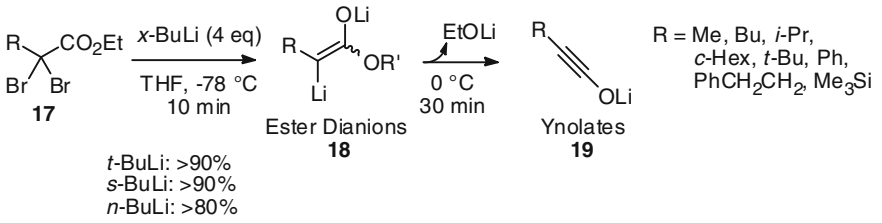


Fig. 5 Efficient preparation of ynolates via ester dianions

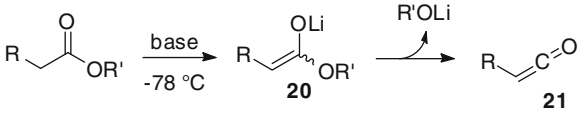


Fig. 6 Conversion of ester enolates into ketenes

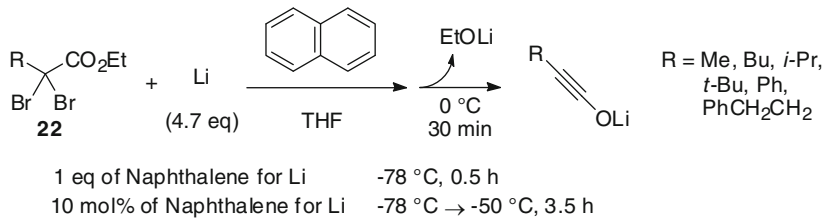


Fig. 7 Preparation of ynolates via reductive lithiation

Although this method is convenient in the laboratory and we can successfully carry out work on up to a 10-g scale, *tert*- or *sec*-butyllithium is somewhat expensive and should be handled carefully, especially on a large scale. With this in mind, we develop a more practical method for the synthesis of ynolates using reductive lithiation (Fig. 7). The dibromo esters **22** are treated with lithium naphthalenide at −78 °C to give the ynolates in good yield. Naphthalene-*catalyzed* reductive lithiation of the dibromo esters **22** is also achieved, providing the ynolates

more efficiently [51]. The synthetic methods for preparing ynolates via the cleavage of ester dianions **18** are not only convenient, but also highly general, because alkyl-, aryl-, and trimethylsilylsubstituted ynolates can be synthesized in good yields.

3 Olefination of Aldehydes

An ynolate reacts with aldehydes **23** at –78 °C, followed by quenching at this temperature, to afford β-lactones **24** [46, 48]. When this reaction is carried out at higher temperature, the (*E*)-α,β-unsaturated carboxylic acid **28** is obtained in good yield, after protonation of the carboxylate **27**, with none of the *Z*-isomer detected (Fig. 8). Further investigation indicates that product **28** is generated by an electrocyclic reaction of the β-lactone enolate **26**, that is, formally, an oxetene. This sequential reaction involving cycloaddition–electrocyclic ring opening reaction is a stereoselective olefination of aldehydes **25**. Although this type of reaction has been reported by Kowalski and Fields [28], they did not follow up this research. Our careful investigations on this reaction reveal that olefination of aldehydes **25** with ynolates provide trisubstituted alkenes **28** with high *E* selectivity in good to moderate yields. Even the thermodynamically unfavorable *E*-olefins can be provided by the ynolates with sterically hindered aldehydes [52].

Since conventional methods such as the Wittig reaction and the Horner–Wadsworth–Emmons reaction are also good at olefination of aldehydes, olefination via ynolates would not necessarily be the first choice for the preparation of unsaturated esters. If, however, one would like to synthesize unsaturated carboxylic acids directly, this method is advantageous. For example, in the synthesis of the natural product bongkrekic acid **32**, olefination of aldehyde **29** giving α,β-unsaturated MOM ester **31** is required (Fig. 9). Since preparation of the Wittig reagent **33** bearing a MOM

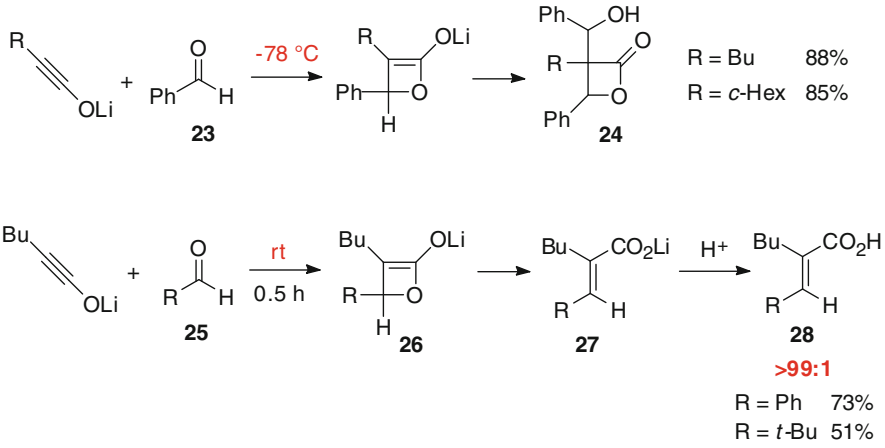


Fig. 8 Olefination of aldehydes with ynolates

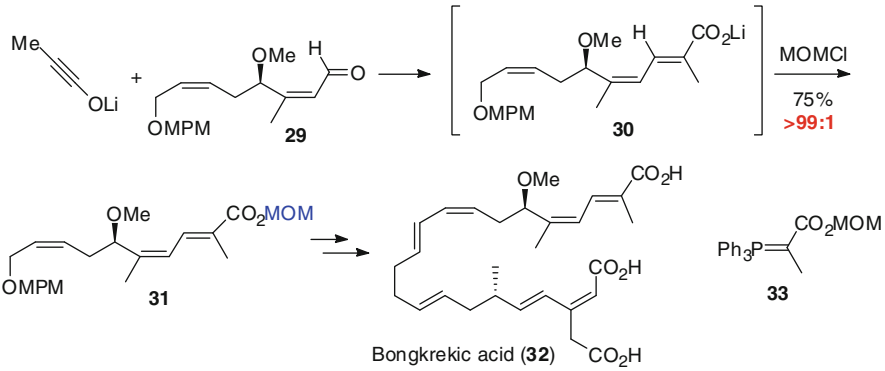


Fig. 9 Synthesis of bongkrekic acid using olefination with ynolate

ester is unsuccessful, the ethyl ester is initially formed by the Wittig reaction, and subsequent hydrolysis, followed by MOM esterification, affords the MOM ester **31**. Alternatively, the aldehyde **29** is olefinated by the ynolate to give an unsaturated carboxylate **30**, which is esterified in situ with MOMCl to afford the desired MOM ester **31** in one pot [53].

4 Olefination of Ketones

Stereoselective olefination of ketones giving tetrasubstituted alkenes is at present very challenging in synthetic organic chemistry; there have been very few reports on successful stereoselective olefination of ketones giving multisubstituted olefins, probably due to the low reactivity compared to aldehydes and much more difficult discrimination of the substituents on the carbonyl group (Fig. 10) [1]. For examples, the Horner–Emmons olefination of acetophenone (**34**) under reflux in EtOH for 24 h gives the corresponding tetrasubstituted olefins **35** in 65% yields with 2:1 *E*/*Z* selectivity (Fig. 11) [54]. The Julia olefination using sulfoxides as a nucleophile provides the tetrasubstituted olefins in low yields [55].

4.1 Unfunctionalized Ketones

Simple unfunctionalized ketones such as aryl alkyl ketones **36** can be olefinated by ynolates to provide tetrasubstituted olefins **37–42** in good to excellent yield (Fig. 12) [56]. While the Wittig and the Horner–Emmons reagents are not suitable reagents for this type of olefination, especially for *tert*-butyl phenyl ketone (**43**), the ynolate affords the corresponding olefin **41** in 74% yield (Fig. 13). Ynolates are actually much better reagents for the olefination of ketones than the conventional

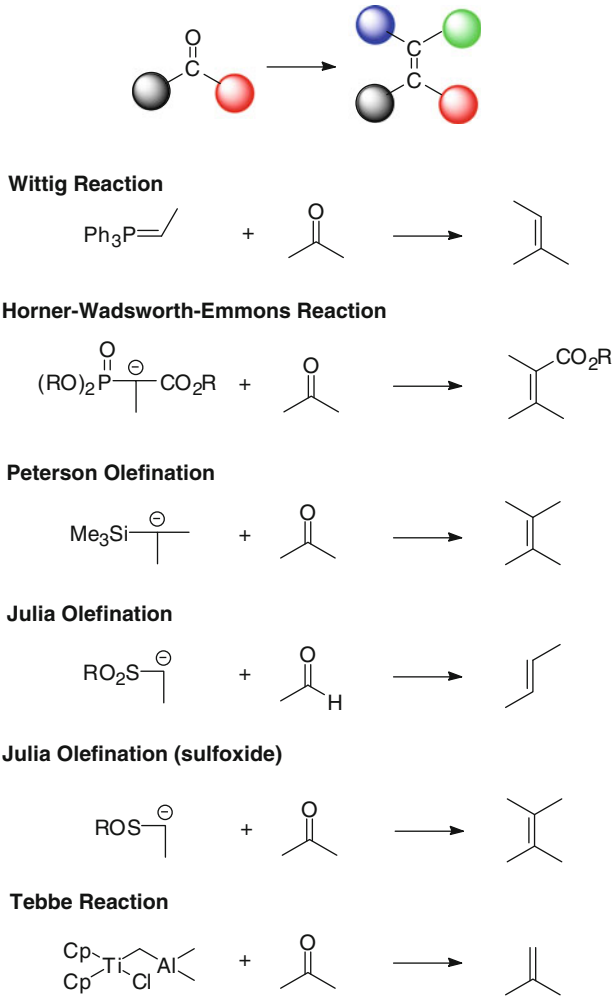


Fig. 10 Representative olefination of carbonyl compounds

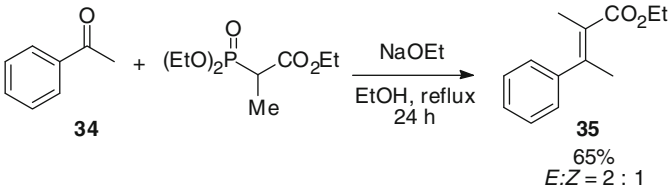
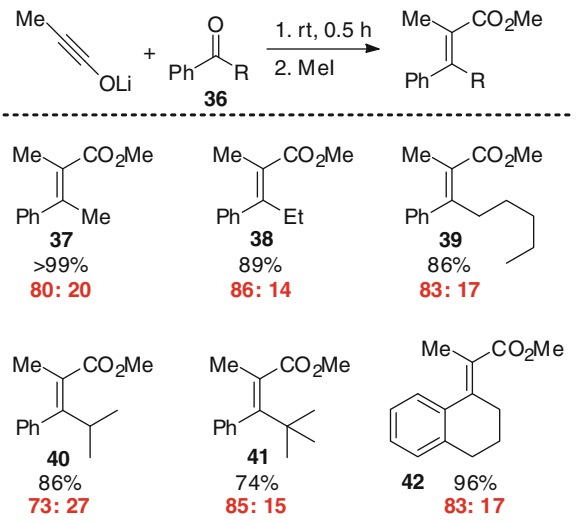


Fig. 11 Horner–Emmons olefination of a ketone providing tetrasubstituted olefins

ones. The *E*/*Z* selectivity (80:20 to 85:15) is much better than that obtained by conventional methods. The aryl group tends to be positioned preferentially *trans* to the carboxylate group, and the alkyl groups are *cis* to it. Instead of carboxylic acids,



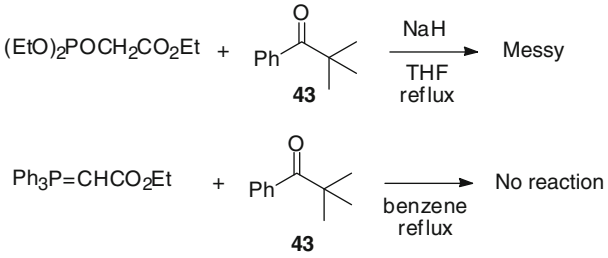


Fig. 12 Olefination of ketones with ynolate

Fig. 13 Olefination of *tert*-butyl phenyl ketone (**43**) by Wittig and HWE reagents

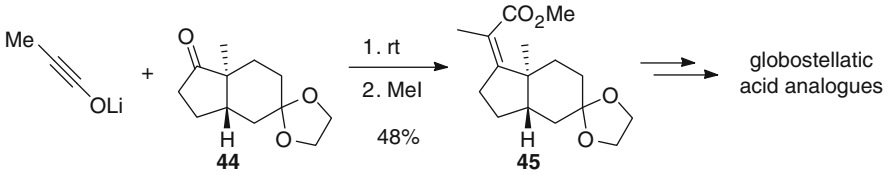


Fig. 14 Synthesis of globostellatic acid analogs

carboxylic acid esters can be isolated in one pot by adding an alkylating reagent like alkyl halide along with HMPA or DMPU to the reaction mixture without loss of selectivity and yield.

This olefination strategy has been used by Kobayashi to synthesize globostellatic acid analogs, an antiangiogenic triterpene derivative from the marine sponge *Stelletta globostellata* (Fig. 14) [57]. Thus ketone **44** is olefinated by ynolate to yield the tetrasubstituted olefin **45**.

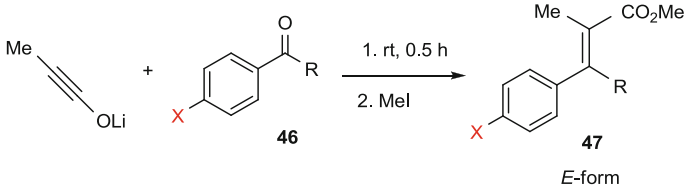
4.2 Stereoelectronic Effect

The *E*/*Z*-selectivity of this olefination is strongly affected by the electronic properties of the substituents (X) of the ketones **46** (Table 1) [58]. The acetophenones with electron-withdrawing groups afford lower *E*-selectivity, and *p*-nitroacetophenone gives the corresponding *Z*-olefin selectively (entry 1). On the other hand, substrates with electron-donating groups at the *para*-position give **47** with higher *E*-selectivity (up to >99:1) (entries 6, 7), as compared to the unsubstituted compounds (X=H, entry 4). In the olefination of *para*-substituted benzophenones (R=Ph), in which both substituents on the carbonyl group are sterically equivalent, the same tendency in the selectivity is observed. It is noteworthy that phenyl substituents are recognized only by remote *para*-substituents. The stereochemistry is controlled by a stereoelectronic, as well as by a steric effect of the substituents.

4.3 Torquoselectivity

The stereoelectronic effect controlling the selectivity is closely related to torquoselectivity. The ring opening of the β-lactone enolates is mechanistically the conrotatory electrocyclic reaction of the oxetene, rather than the "forbidden" β-elimination [59], in which the π-orbital of the enolate C=C bond and the σ*-orbital of the disconnecting C–O bond are fixed in an orthogonal position, and thus the torquoselectivity concept should be taken into account. Thermal ring opening of cyclobutenes giving butadienes has been well studied experimentally [60, 61] and theoretically (Fig. 15) [62, 63]. In this reaction, the *E*/*Z* selectivities are determined by the torquoselectivity. Thus, the electron-donating substituents (D), such as OMe, Me, NH_2, and BH_3^-, rotate outward preferentially and the electron-accepting substituents (A), such as CHO, SiH_2F, $SiHF_2$, and BH_2, rotate inward. The torquoselectivity is

Table 1 Stereoelectronic effect on the olefination of *para*-substituted acetophenones and benzophenones



		Acetophenone (R=Me)		Benzophenone (R=Ph)	
Entry	X	*E*/*Z*	Yield (%)	*E*/*Z*	Yield (%)
1	NO_2	25:75	68	30:70	95
2	Cl	70:30	94	45:55	>99
3	F	80:20	86	55:45	>99
4	H	80:20	>99	–	>99
5	Me	88:12	>99	60:40	>99
6	MeO	93:7	98	70:30	>99
7	Me_2N	>99:1	51	86:14	>99

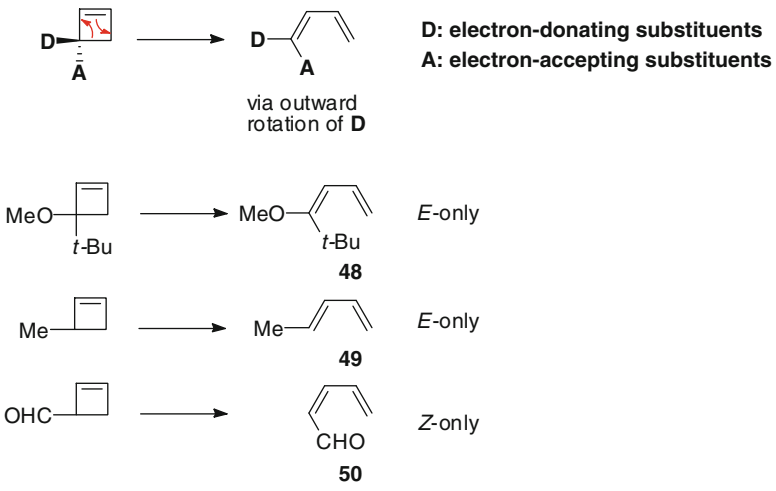


Fig. 15 Torquoselectivity in the electrocyclic ring-opening of cyclobutenes

explained by the orbital interactions between the breaking C–C bond and some bond orbitals on the substituents. In the transition states of the ring opening, repulsive interaction between the HOMO of the donor substituent and the cleaving C–C σ-orbital leads the substituents to outward rotation, while interaction between the vacant orbital of the accepting substituent and the cleaving C–C σ-orbital makes the substituents rotate inward. For examples, since a methoxy group is relatively electron-donating compared to a *tert*-butyl group, the methoxy group rotates outward preferentially to give (*E*)-1,3-diene **48**. Likewise, the methyl group exhibits preference for outward rotation to give *E*-olefin **49**. On the other hand, the formyl group rotates inward (**50**) exclusively, due to the electron withdrawing character of the substituent.

Oxetene and cyclobutene are mutually isoelectronic and there are few theoretical studies on substituent effects in the ring opening of oxetenes, although there have been several reports on molecular orbital studies of oxetene ring openings [64, 65]. Therefore, if the cyclobutene is replaced by the oxetene, this concept provides a rational explanation for the olefination with ynolates (Fig. 16). Theoretical calculations on the transition states revealed the strong interactions between the breaking C–O σ orbital in the oxetene and the π (π*) orbitals of the aromatic ring in the transition states (Fig. 17). Since the phenyl group has a π-orbital with a high energy level of the occupied orbital, it is a better electron-donating group than the alkyl group (**51**→**52**). However, it depends on the substituents. For examples, the *p*-nitro substituent on the aromatic ring alters its property to electron accepting in torquoselectivity. The transition state leading to the *Z*-olefins would be stabilized by the overlap of the orbitals of the breaking C–O σ bond with the π*-orbitals, in which the energy level of the antibonding orbital is lowered by the electron-withdrawing substituents (X) (**53**→**54**). The σ* orbitals are also important acceptors in the torquoselectivity [66, 67]. Since the C–CH_3 σ*-orbital is reported to be more electron accepting than the C–H σ*-orbital [68], a *tert*-butyl group in **55** would be more electron accepting than a methyl group, which would work as an electron-donating group. Therefore, the *tert*-butyl group preferentially rotates inward (**56**) when compared to a methyl group (Fig. 18) [69]. In order to

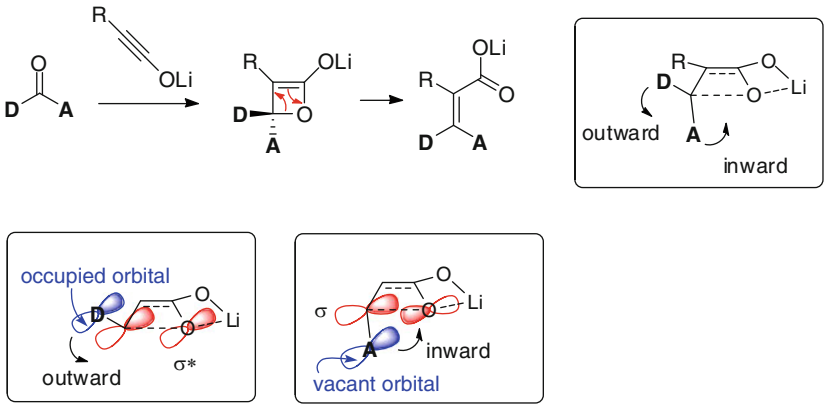


Fig. 16 Torquoselectivity in the electrocyclic ring-opening of oxetenes

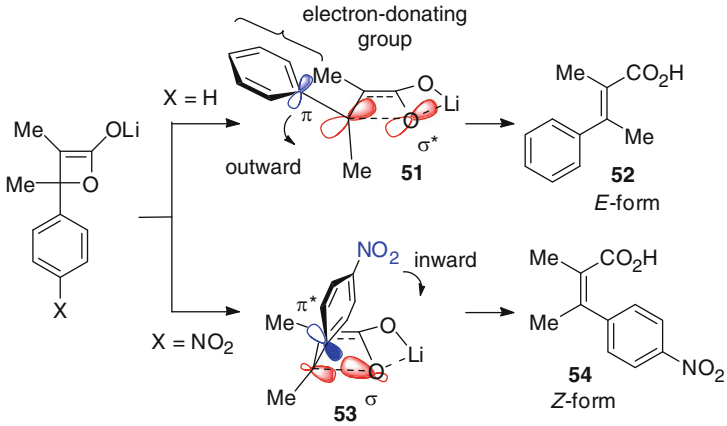


Fig. 17 Torquoselectivity in the transition states of the ring-opening for olefination of acetophenones

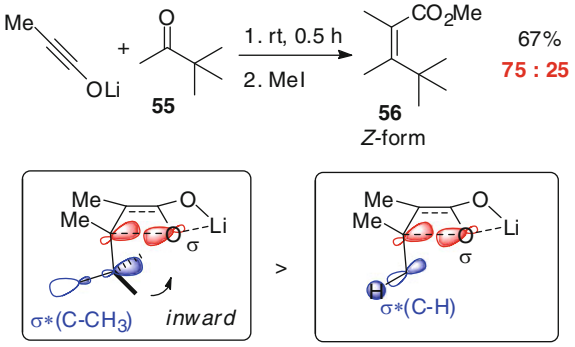


Fig. 18 The σ*-orbital interactions in the transition states of the ring-opening

clarify the torquoselectivity, careful considerations of the secondary orbital interactions would be necessary.

4.4 α-Alkoxyketones

For good stereocontrol in the olefination of ketones with ynolates, it would be required that groups of quite different bulkiness and/or electronic properties are attached to the carbonyl group. Simpler ketones like 2-butanone are less discriminating in this process. If both substituents on the ketones should be distinguished, strong stereocontrolling directing groups for olefination are essential in the ketones. Ethereal oxygens often work as a hard Lewis basic directing group by coordination to the Lewis acidic metal cations. Since chelation control is expected, α-alkoxyketones are suitable candidates as the substrate. The α-alkoxy and α-trialkylsiloxy acyclic ketones **57** provide the olefins **58–62**, respectively, with high *Z*-selectivity by the torquoselective olefination with ynolates (Fig. 19). The α-trialkylsiloxy cyclic ketones afford the olefins **63** and **64** with low to excellent stereoselectivity. This selectivity depends on the conformation of the siloxy group; for example, the axially oriented siloxy group induces a high *Z*-selectivity (**65**→**66**) but the equatorially oriented group does not (**67**→**68**) (Fig. 20).

The mechanism of olefination can be deduced by consideration of orbital interactions to proceed via torquoselective olefination, rather than chelation control, for the following reasons: (1) the sterically hindered siloxy (**60**) and the poor Lewis-basic phenoxy groups (**61**) are also effective for high *Z*-induction; (2) in the presence of a crown ether, the selectivity still remains high; and (3) an axially oriented siloxy group (**65**), which is far from a lithium cation, induces a high *Z*-selectivity. Theoretical calculations indicate that the transition state of inward rotation is stabilized by an orbital interaction between σ(C–O) and σ*(C–OR) orbitals (Fig. 21) [70]. The higher

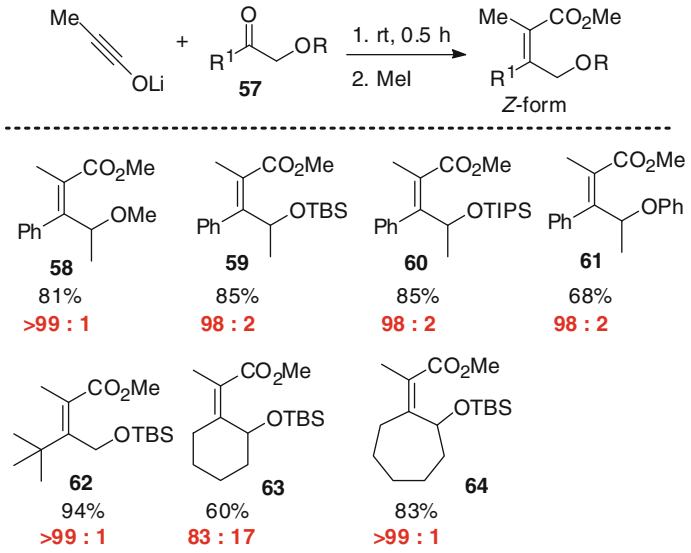


Fig. 19 Olefination of α-alkoxy and α-siloxy ketones

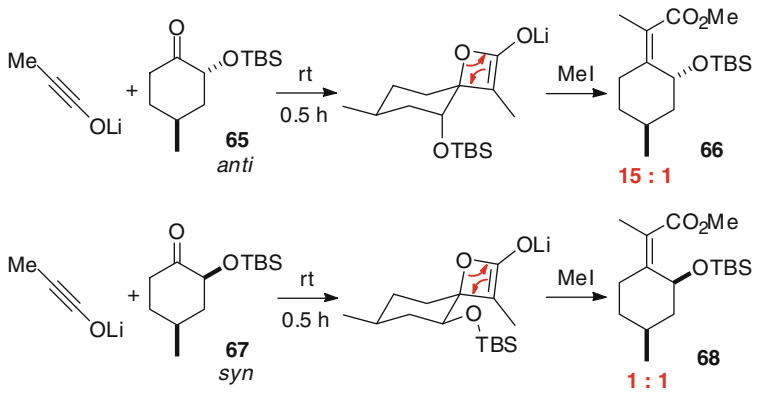


Fig. 20 Olefination of α-trialkylsiloxy cyclic ketones

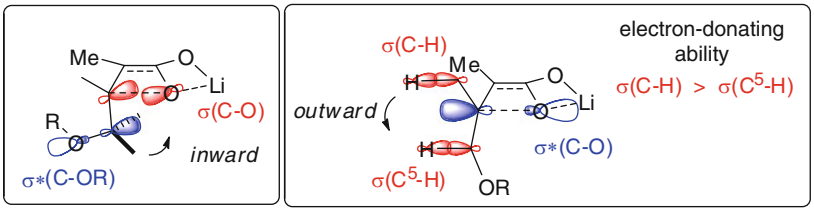


Fig. 21 Secondary orbital interactions in the transition states on olefination of α-alkoxy ketones

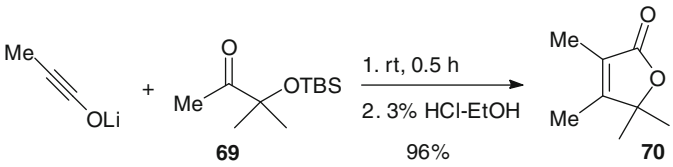


Fig. 22 Synthesis of γ-butenolides

energy level of σ(C–H) orbital at α-position is more important. Namely, the σ(C–H) orbital on the alkoxy-substituted methyl group is at lower energy level than that on the non-substituted methyl group. Therefore, the simple alkyl substituent tends to rotate outward rather than the alkokymethyl group.

The products, *Z*-α-siloxyacrylic acids, are easily converted into polysubstituted γ-lactones **70** by acidic treatment. This transformation can be carried out in one pot from the starting ketones **69** (Fig. 22).

4.5 α-Amino, α-Thio, α-Selenoketones

In a similar fashion, olefination of α-amino ketones also induces good *Z*-selectivity. As shown in Fig. 23, the reaction of the ynolates with the α-amino ketone **71** gives the γ-amino unsaturated carboxylates **72**, which are treated with mesyl chloride to provide the unsaturated lactams **73** in good yield, without any detection of minor isomers.

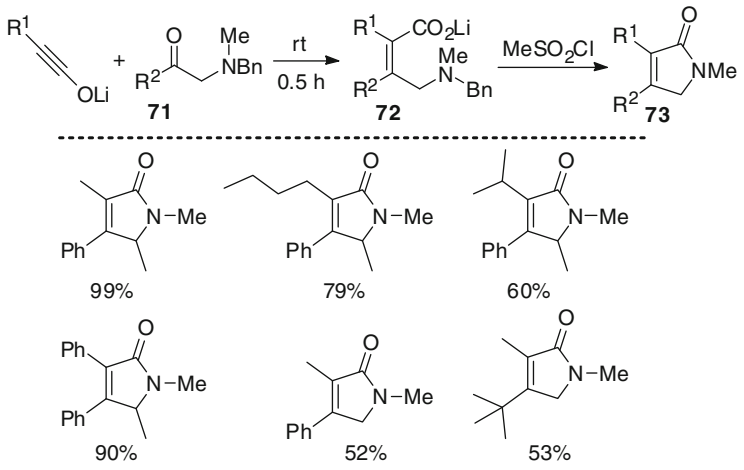


Fig. 23 Olefination of α-aminoketones affording γ-butyrolactams

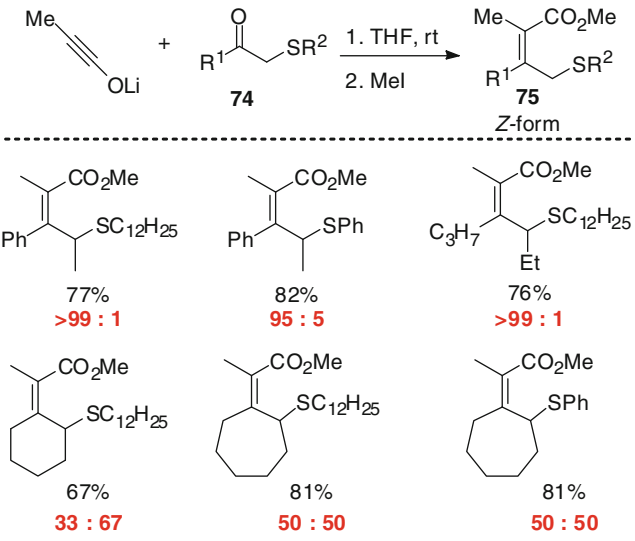


Fig. 24 Olefination of α-thioketones

This concept can be applied to the olefination of α-thioketones if the secondary orbital interactions between the breaking C–O σ orbital and the C–X σ* orbital are critical for the selectivity rather than chelation control. Olefination of α-dodecylthio- and α-phenylthioketones **74** furnishes the tetrasubstituted alkenes **75** with good to excellent *Z*-selectivity (Fig. 24) [71]. In contrast to the acyclic ketones and α-siloxyketones, 2-phenylthiocycloalkanones give no selectivity, probably because the conformation of the directing group (RS–) might be more strongly fixed in the equatorial position due to the larger A-value of alkylthio group than that of the

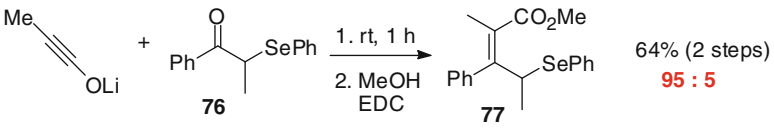


Fig. 25 Olefination of α-selenoketone

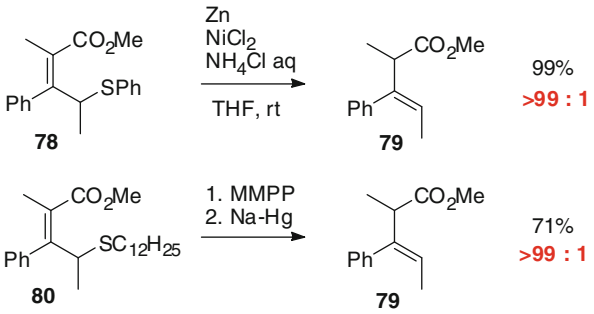


Fig. 26 Desulfurization of multisubstituted allylsulfides

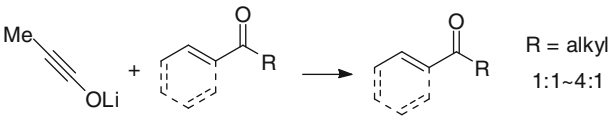


Fig. 27 Stereoselectivity for olefination of alkyl aryl ketones and enones

corresponding alkoxy group. In a similar fashion, α-selenoketones **76** are olefinated to give **77** with good *Z* selectivity (Fig. 25).

Desulfurization of the multisubstituted allylsulfides **78** and **80** results in isomerization of the olefin to give the less substituted one **79**, probably due to the steric strain in the transition states of the protonation of the allylic radical or anion species (Fig. 26).

4.6 Alkynyl Ketones

The above-mentioned highly stereoselective olefination of ketones is controlled by heteroatom-assisted torquoselectivity. The effect of nonpolarized carbon functional groups on torquoselectivity would also work as a controlling factor. C–C double bonds present in substituents such as alkenyl and aromatic groups do not afford sufficient selectivity in the olefination of the corresponding alkyl ketones (Fig. 27). The energy level of the HOMO and LUMO in the C=C bond would not be high or low enough to achieve high selectivity.

In contrast, the C–C triple bond shows excellent effect on torquoselectivity. Alkynyl alkyl ketones **81** are olefinated by ynolates to afford the tetrasubstituted olefins **83** in good *E*-selectivity (Fig. 28) [72]. In the electrocyclic reaction of **82**, the alkynyl group prefers outward rather than inward rotation over the alkyl and alkenyl

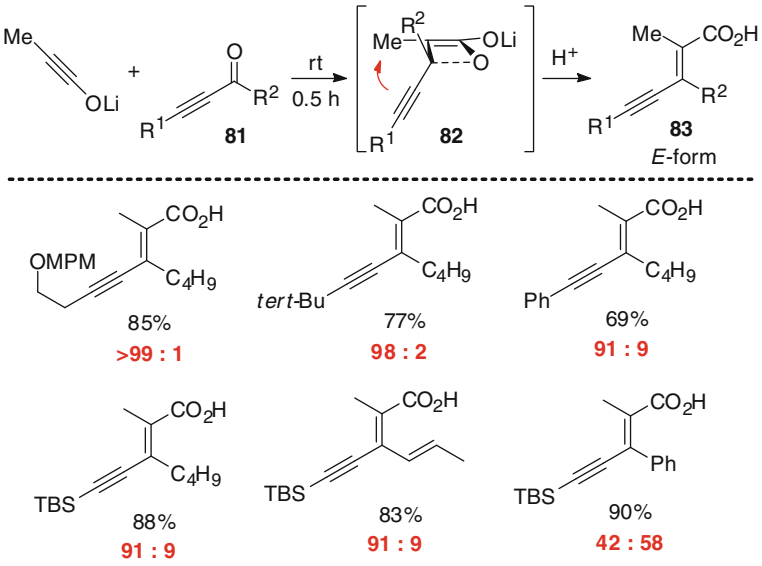


Fig. 28 Olefination of alkynyl ketones with ynolates

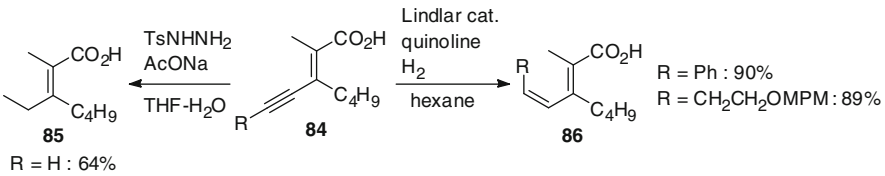


Fig. 29 Reduction of the C–C triple bond

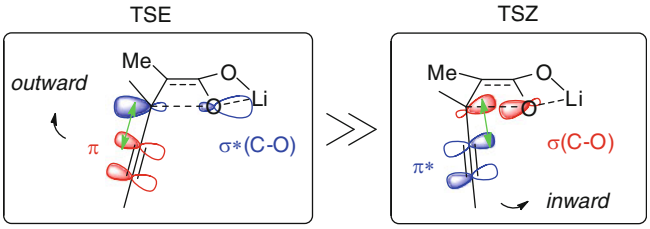


Fig. 30 Secondary orbital interactions in the transition states for olefination of alkynyl ketones

groups, and the substituent on the terminal position of the ethynyl group has a slight effect on the torquoselectivity. The triple bond of the resulting conjugate enyne compounds **84** can be reduced into alkyl (**85**) and *cis*-alkenyl groups (**86**) (Fig. 29).

Theoretical calculations (B3LYP/6-31G(d)) for the ring-opening transition states of the oxetene reveal that the transition state to the *E*-form (TSE) is 8.3 kJ/mol more stable than the transition state to the *Z*-form (TSZ). In addition, the natural bond

orbital (NBO) analysis indicates the secondary orbital interactions between the π-orbital of the alkyne and the σ*-orbital of the breaking C–O bond, and between the π*-orbital of the alkyne and the σ-orbital of the breaking C–O bond (Fig. 30).

5 Olefination of Acylsilanes, Acylgermanes, and Acylstannanes

5.1 Olefination

Acylsilanes, acylgermanes, and acylstannanes are potential precursors of alkenylsilanes, alkenylgermanes, and alkenylstannanes, which are important and powerful synthetic tools [73, 74]. However, practical methodology for their preparation via olefination had not been reported. Olefination of the acylsilanes **87** with ynolates provides the β-silyl-α,β-unsaturated esters **88** in high yields with excellent *Z*-selectivity (Fig. 31). In most cases, the *E* isomers cannot be detected by ^{1}H NMR and HPLC at all. This is the first general method for the stereoselective synthesis of tetrasubstituted olefins [75].

Theoretical calculations and NBO analysis suggest that this torquoselectivity is due to orbital interactions of the breaking σ(C–O)–σ*(Si–C) in the transition state of the inward rotation during the ring opening of the β-lactone enolate (Fig. 32). This is in good agreement with the results obtained from the ring opening of silylcyclobutenes [66, 67, 76–79]. However, the torquoselectivity of silyloxetenes is much higher than that of silylcyclobutenes. One reason for the different selectivity would be the reaction temperature. The silyloxetene ring-opens at room temperature although the silylcyclobutene does so at higher temperature. Another reason would be the interaction between the nonbonding orbital of oxygen on the oxetene

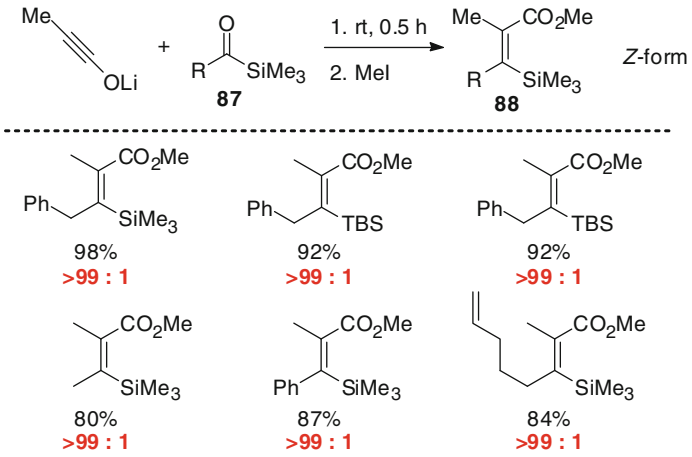


Fig. 31 Olefination of acylsilanes

Fig. 32 Two orbital interactions stabilizing the transition state to the Z-form

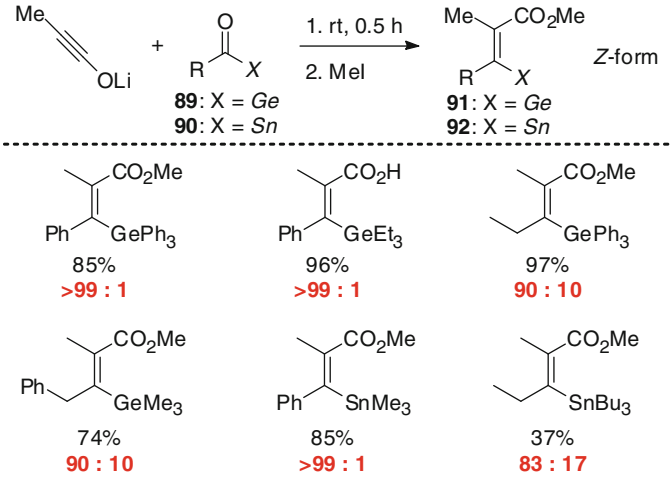


Fig. 33 Olefination of acylgermanes and acylstannanes

and σ*(Si–C), which is indicated by the NBO analysis. This secondary orbital interaction is also an important factor for stabilization of that transition state [69].

In the same way, acylgermanes **89** and acylstannanes **90** are olefinated with ynolates to give *Z*-alkenylgermanes **91** and *Z*-alkenylstannanes **92** (Fig. 33). Although the *E*/*Z* ratios are a little lower than that of acylsilanes **87**, satisfactory ratios are obtained [80].

5.2 *Properties and Reactions of Intramolecularly Activated Alkenylsilanes, Alkenylgermanes*

The importance of the torquoselective olefination is illustrated in Fig. 34 for the particular case in which a multisubstituted alkenylsilane is converted to various kinds of multisubstituted olefins. The silyl-substituted allyl alcohol **93** is allylated to give the 1,4-diene **94**, and the iodoalkene **95**, prepared by desilyliodination of **93**, is subjected to palladium-catalyzed cross-coupling reactions (the Heck reaction, Stille coupling) to afford the dienes **96** and **97** without *E*/*Z* isomerization.

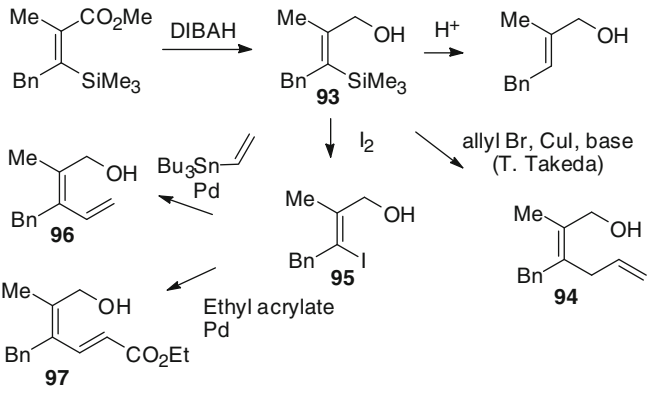


Fig. 34 Various conversions of alkenylsilanes into multisubstituted olefins

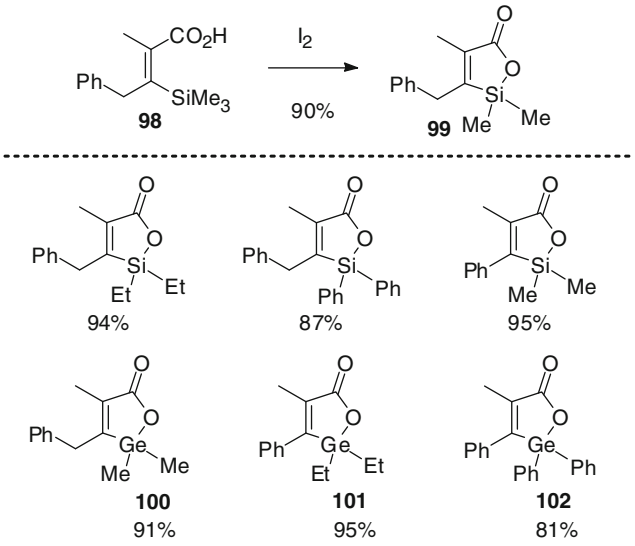


Fig. 35 Synthesis of silalactones and germalactones

5.3 *Hypervalent Silicones and Germanes*

The alkenylsilane **98** reacts with iodine to afford the silalactone **99**, with elimination of iodomethane, in good yield (Fig. 35) [81]. This unexpected process involves the mild oxidative cleavage of a silicon–carbon bond which should otherwise be stable. The silicon–carbon bond is activated by hypervalency induced by intramolecular coordination of the carbonyl oxygen to the silicon atom. This is supported by the observation that the O–C bond length is shorter than that of the sum of the van der Waals radii (3.35 Å) in the X-ray crystal structure analysis of **98**. The TBP value [82] is 20%, meaning that it is not a perfect trigonal bipyramidal structure but is on the way

to this structure. The C–Si bond is therefore weakened and can be cleaved under mild conditions via a push–pull mechanism, as depicted in Fig. 36. In the same manner, the alkenylgermanes are transformed into germalactones **100**–**102** in good yields. These compounds are very useful synthons, as described in the next sections.

5.4 Reactions of Silalactones

The carbonyl group on the silalactone **99** is reduced by lithium aluminum hydride to afford 1,2-oxasilole **103**. However, Grignard reagents attack the silicon atom to provide β-silylacrylic acids **104** (Fig. 37). Repetition of the oxidative cleavage and the Grignard reaction will potentially lead to other alkenylsilanes bearing various kinds of carbon substituents on the silicon. The palladium-catalyzed cross coupling of silalactones **99** with aryl halides can be carried out without using fluoride anion to afford the corresponding coupling product **105**. For a review on fluoride-free Hiyama reaction, see [83].

5.5 Pd-Catalyzed Fluoride-Free Cross Coupling of Alkenylsilanes and Germanes

The coupling reactions of alkenylsilanes generally require activation of the silicon due to the low reactivity of the C–Si bond. Introduction of heteroatoms on the

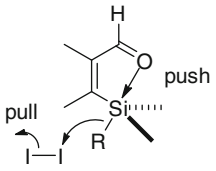


Fig. 36 Push–pull mechanism

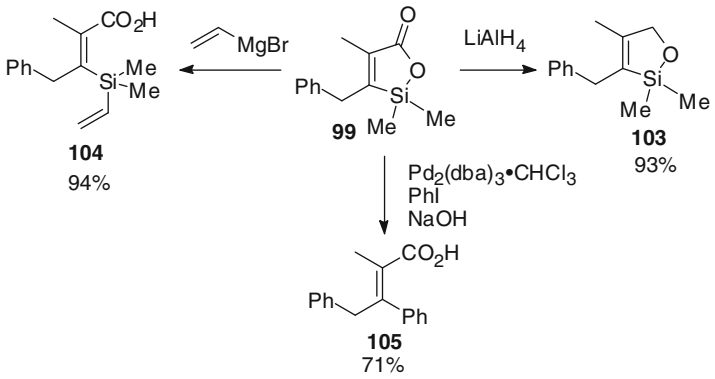


Fig. 37 Reactions of silalactone

silicon [84, 85] and/or the addition of fluoride ion to the reaction are standard activation methods to form reactive hypervalent silicates. The palladium-catalyzed cross coupling of the alkenylsilane **98** with aryl iodides (the Hiyama coupling) [86–90] produces the coupling product **105** in good to moderate yield. This reaction can be carried out without using fluoride ion (Fig. 38), since the alkenylsilane **98** is intrinsically activated by forming hypervalency [91–97]. This reactivity can be exploited in an *E*/*Z*-selective synthesis of fully-carbon-substituted olefins. However, the generation of protodesilylation side products could not be prevented. This is the reason why less than excellent yields are obtained.

The intrinsically activated alkenylgermanes **106** are more reactive in the cross coupling reaction (Fig. 39). The reaction is dependent on the palladium catalyst and, as a ligand, Pd(P*t*-Bu_3)$_2$ works very efficiently in NMP to afford the desired coupling product **107** in better yield without the generation of the protonated byproducts, which generally cause poor yields in this type of coupling reaction.

This coupling reaction of alkenylgermanes can be applied to the synthesis of estrogen receptor modulator tamoxifen (**112**), which is used in the clinical treatment of estrogen-dependent breast cancer (Fig. 40). The benzoyl triethylgermane (**108**) is olefinated with ynolate to give the alkenylgermane **109**, which is coupled

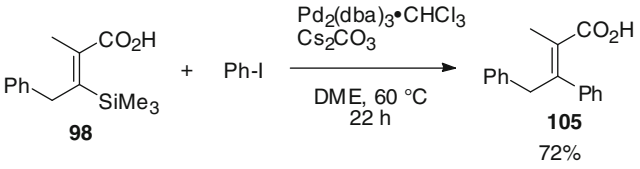


Fig. 38 Palladium catalyzed cross-coupling of alkenylsilane

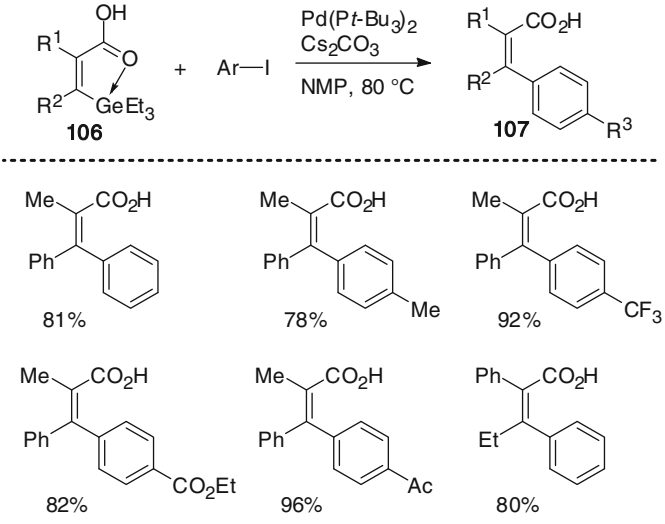


Fig. 39 Cross coupling of hypervalent alkenylgermanes

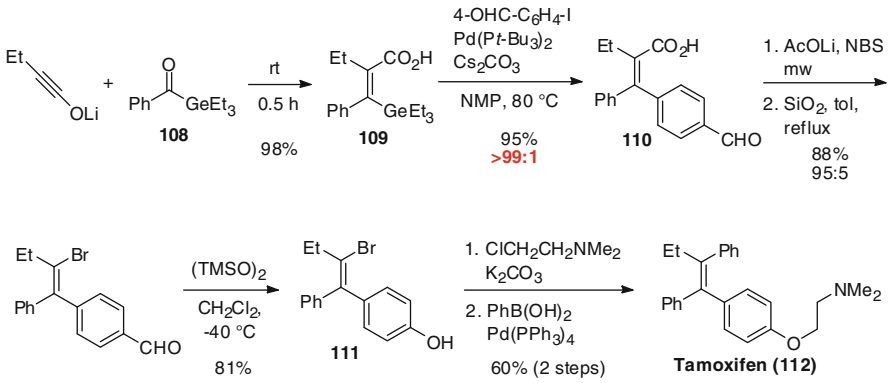


Fig. 40 Synthesis of tamoxifen

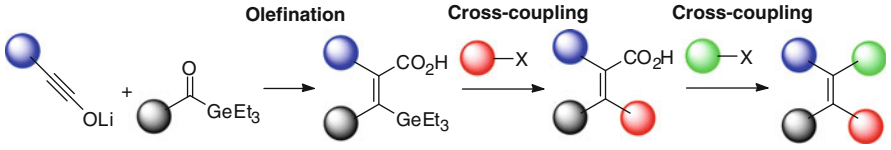


Fig. 41 Diversity oriented synthesis of tetrasubstituted olefins

with aryl iodide to afford the tetrasubstituted alkene **110**. A modified Hunsdiecker reaction, followed by the Dakin reaction, leads to bromoalkene **111**, which is subjected to the Suzuki–Miyaura coupling to afford tamoxifen (**112**). This reaction sequence for the preparation of the tetrasubstituted olefins can be regarded as an introduction of all four substituents separately on the olefin (Fig. 41).

6 Olefination of Esters

6.1 Olefination

The olefination of ester carbonyl groups has generally been unsuccessful due to the lower reactivity of the ester function and the elimination of alkoxide. Metal carbenoids, such as the Tebbe reagents, accomplish this transformation, but they are limited to the preparation of simple unfunctionalized enol ethers. On the other hand, the highly stereoselective synthesis of tetrasubstituted, functionalized (*E*)-enol ethers **115** via olefination of esters **113** with ynolates is successfully achieved (Fig. 42) [98]. Aliphatic esters afford excellent *E*-selectivities (**116–118**), whereas esters of aromatic carboxylic acids give good to moderate selectivity (**119–121**), which depends on the electronic properties of the substituents on the aromatic ring. This torquoselectivity can be rationalized by the fact that the ethoxy group in **114** preferentially rotates outward because of its electron-donating property.

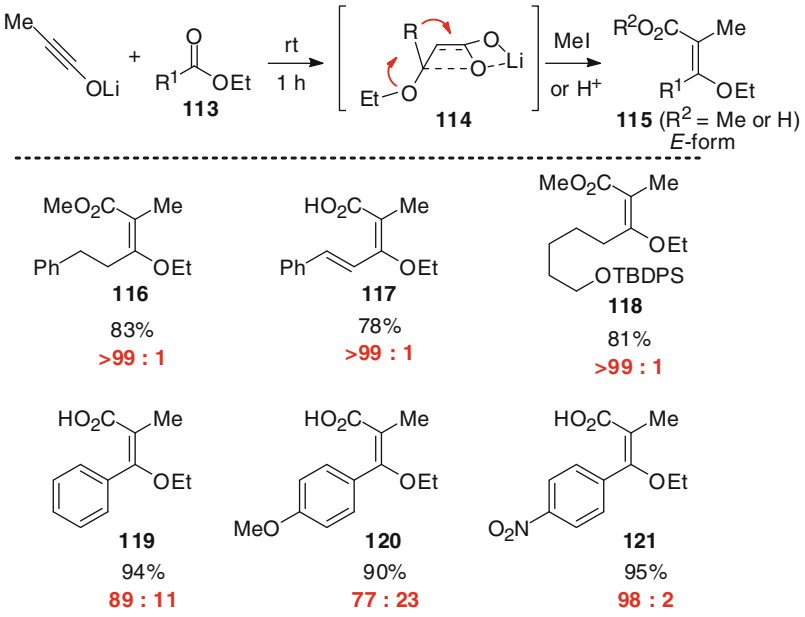


Fig. 42 Olefination of ester carbonyl

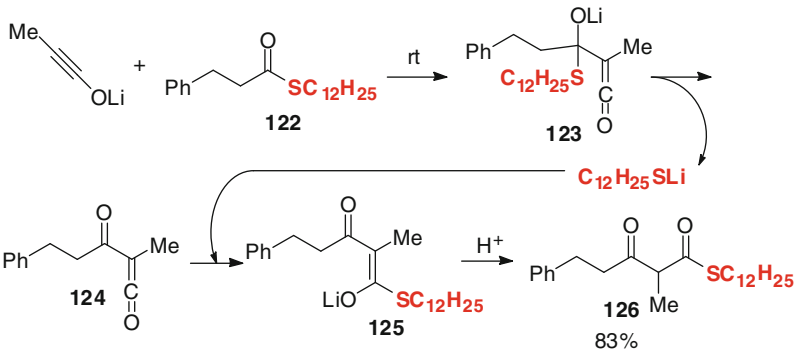


Fig. 43 Homologation of thioesters

6.2 *Homologation*

In the olefination of an ester carbonyl, the elimination of alkoxide, leading to a ketene, causes low yield. If this "side reaction" becomes the major reaction course, it would be a new reaction other than olefination. The reaction of thiol esters (thiolates are better leaving groups than alkoxides) with lithium ynolates takes place by a route different from that for alcohol esters (Fig. 43). Thiol esters **122** undergo a two-carbon homologation to afford β-keto thiol esters **126** in good yield.

Intermediates **123** undergo a two-step rearrangement to a β-keto thiol ester enolate **125**, via elimination of thiolate to yield a ketene **124**, followed by the nucleophilic attack of the thiolate on **124**. Finally, the homologated β-keto thioester **126** is obtained on acidification of the reaction mixture. This is a two-carbon homologation via insertion of ynolate into the C–S bond of thiol esters.

6.3 Synthetic Applications

The enol ethers thus produced are expected to be very useful in synthetic organic chemistry. Herein, the Nazarov reaction is demonstrated for an application of the products.

The Nazarov reaction is a 4π electrocyclic reaction giving cyclopentenones and mediated by acids (Fig. 44) [99–101]. Although it was discovered a long time ago, the harsh conditions and the poor regiochemistry of the alkene in the cyclopentenone product have kept the reaction from enjoying a wider use in synthetic organic chemistry. In recent years, improved Nazarov reactions, such as the Lewis acid catalyzed reaction and a substituent-controlled regioselective reaction, are reported, and are being widely used [102–110].

The *(E)*-β-alkoxy divinyl ketones **129**, potential Nazarov reaction precursors, are prepared according to the torquoselective olefination methodology with ynolates (Fig. 45). For example, ethyl 3-phenylpropionate (**127**) is olefinated by the ynolate to afford the β-alkoxy-α,β-unsaturated acid **128** with high *E*-selectivity. The acid **128** is converted into the Weinreb amide, which is subjected to alkenylation to provide the β-alkoxy divinyl ketone **129** in good overall yield.

The *(E)*-β-alkoxy divinyl ketones **129** are treated with a trace amount of triflic acid at ambient temperature to afford α-alkoxycyclopentenone **130** in excellent

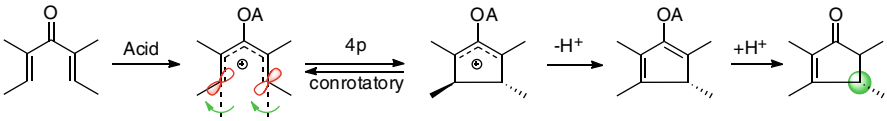


Fig. 44 Classical Nazarov reaction

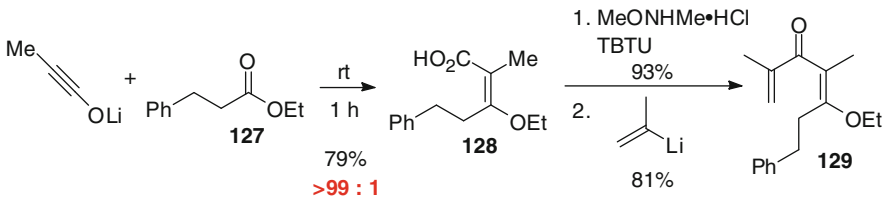


Fig. 45 Synthesis of *(E)*-β-alkoxy divinyl ketone

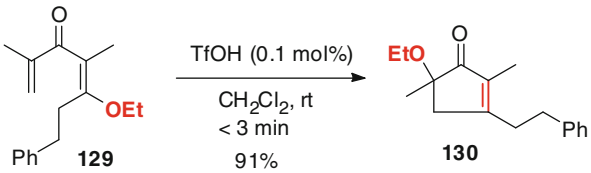


Fig. 46 Acid-catalyzed Nazarov reaction of β-alkoxy divinyl ketone

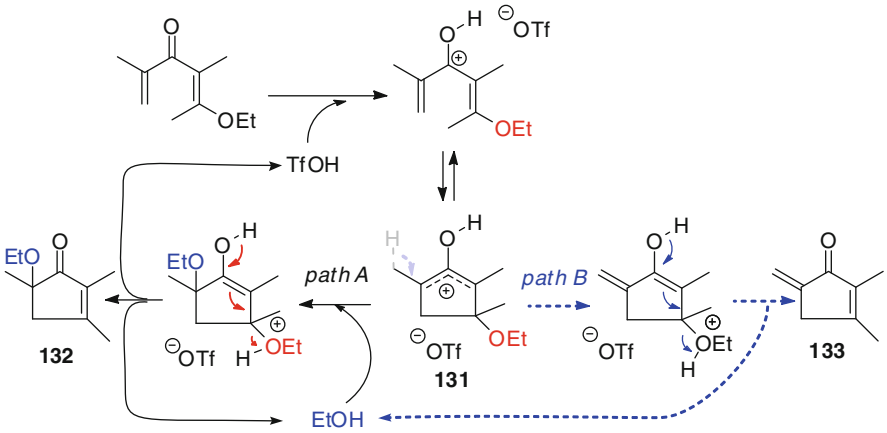


Fig. 47 Proposed mechanism on Nazarov reaction of β-alkoxy divinyl ketone

yield within 1 min (Fig. 46) [111]. This is an unexpected result for the following reasons. In most of the modern catalytic Nazarov reaction, the α-*alkoxy* divinyl ketones are used as the substrate, and the β-alkoxy divinyl ketones were believed to be poor substrates, because the cyclopentenyl cation intermediate is destabilized by the β-alkoxy group, and thus the electrocyclization does not proceed. However, in this case, the methyl groups beside the carbonyl stabilize the oxyallyl cation intermediate **131** via hyperconjugation, and thus the cyclization quickly proceeds (Fig. 47). Furthermore, the alkoxide migration enhances the reaction and controls the regioselectivity of the double bond in the five-membered ring **132** (path A). However, this migration is not intramolecular, but intermolecular, according to crossover and isotope-labeling experiments. The initial alkoxide (or alcohol) would be generated by the side reaction (path B) giving the α-methylenecyclopentenoids **133**.

The α-methylene cyclopentenones of the side products are also often found in natural products as bioactive moieties. In the absence of nucleophiles, the α-exo-methylene products become the major products. When the Nazarov reaction with **134** is carried out in the presence of *tert*-butanol, which is expected to displace the other nucleophile, the *exo*-methylene cyclopentenone **135** is produced as a major product (Fig. 48).

Using this protocol, antibiotic antitumor natural product xanthocidin (**136**) is synthesized as shown in Fig. 49 [112].

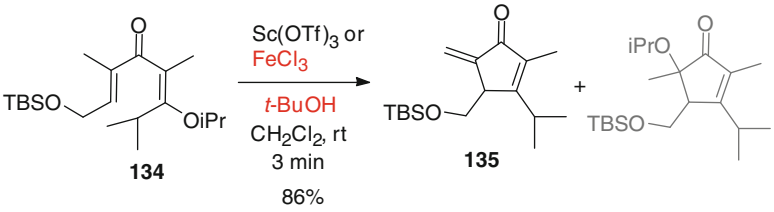


Fig. 48 Selective synthesis of α-methylene cyclopentenone

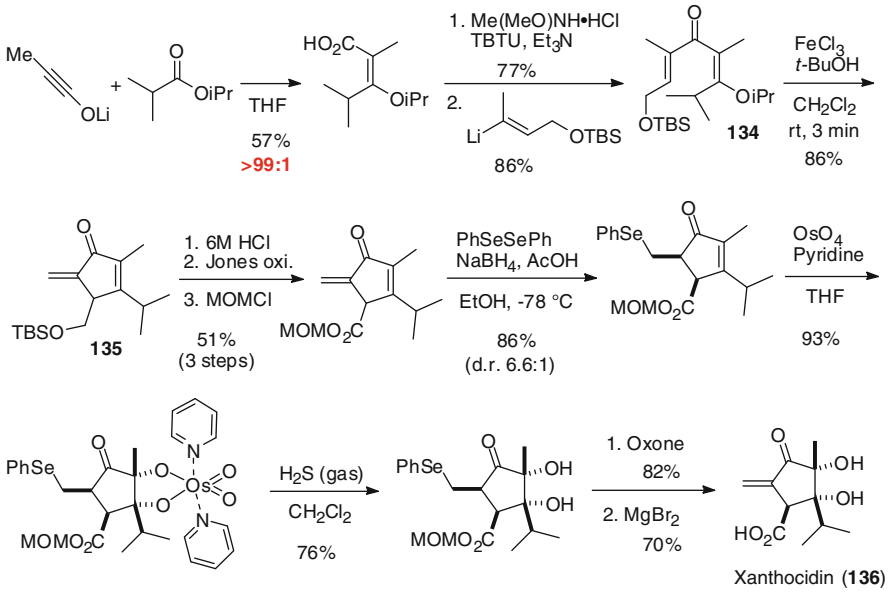


Fig. 49 Synthesis of xanthocidin

Catalytic asymmetric Nazarov reactions have been reported by Aggarwal [113], Trauner [114, 115], Togni [116], Rueping [117, 118], and Tius [119, 120]. Most of these successful results used bidentate-type substrates bearing an α-oxy group (mostly dihydropyran-2-yl, **137**) or α,β-carbonyl unit (e.g., **138**) for fixing the metal ternary complex by chelation as well as for stabilizing the intermediates. Chiral Lewis acid-catalyzed asymmetric Nazarov reaction of β-alkoxy divinyl ketones **139**, which is a monodentate-type substrate, is also possible. As shown in Fig. 50, Pybox/Ph-Sc(OTf)$_3$ complex catalyzes the reaction to afford the cyclized product **140** up to 91% ee in the presence of sterically hindered alcohol [121]. In this reaction, a quaternary chiral carbon is created in the step of addition of the alkoxide to the intermediate oxyallyl cation. The stereochemical course of the reaction can be rationalized by assuming the reacting complex depicted in Fig. 51.

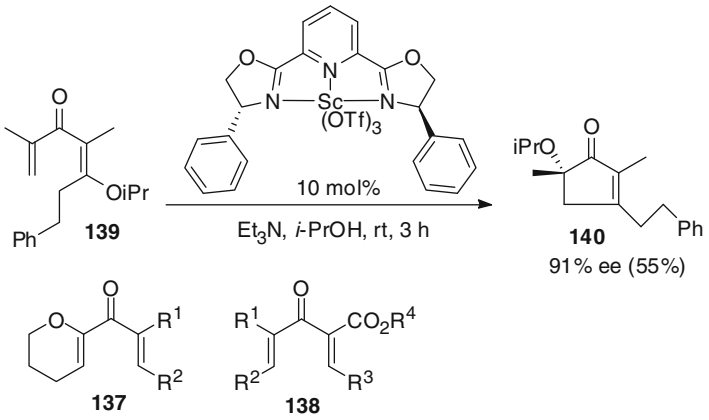
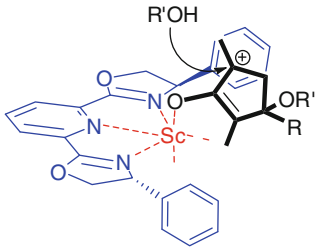


Fig. 50 Catalytic asymmetric Nazarov reaction

Fig. 51 Proposed model of asymmetric induction



7 Olefination of Aldimines

A silyl-substituted ynolate **141** undergoes cycloaddition to *N*-sulfonyl aldimines **142**, followed by ring opening, to afford the α,β-unsaturated amide **143** at 20 °C (Fig. 52) [39]. This stereoselectivity is unexpected for the torquoselective olefination. The steric interaction between bulky Me_3Si and the phenyl groups may be critical. *N*-*o*-Methoxyphenylaldimines **144** with ynolates at room temperature produce α,β-unsaturated amides **145** in good yield with high *E*-selectivity (Fig. 53) [122]. Since the double adduct **146** is produced as an intermediate, the process involves the retro-Mannich reaction.

8 Conclusion

Since the torquoselectivity concept was proposed in the 1980s, this concept has been used in various aspects of organic chemistry. Most of these investigations involved syntheses of 1,3-dienes via electrocyclic ring-opening reactions of

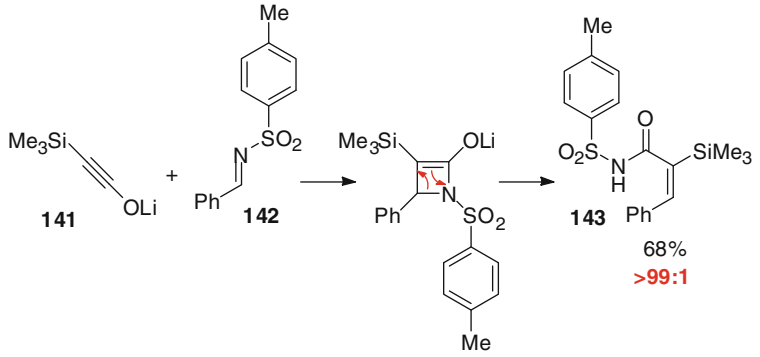


Fig. 52 Olefination of *N*-sulfonyl aldimine

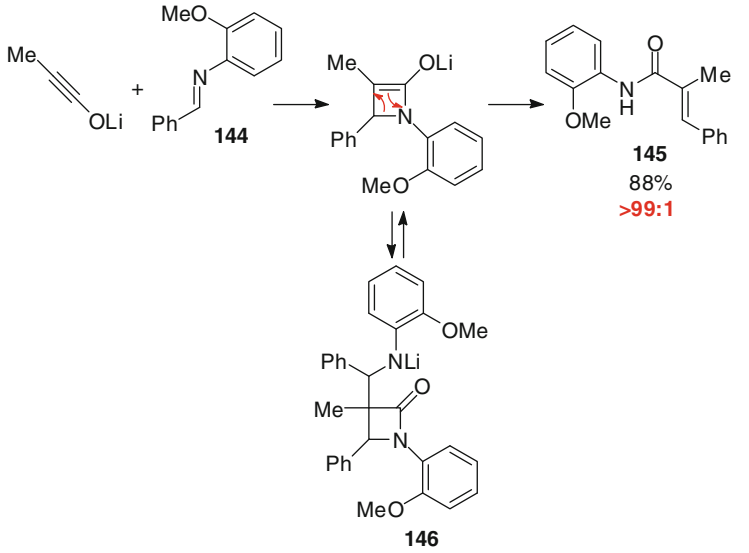


Fig. 53 Olefination of *N*-*o*-methoxyphenyl aldimine

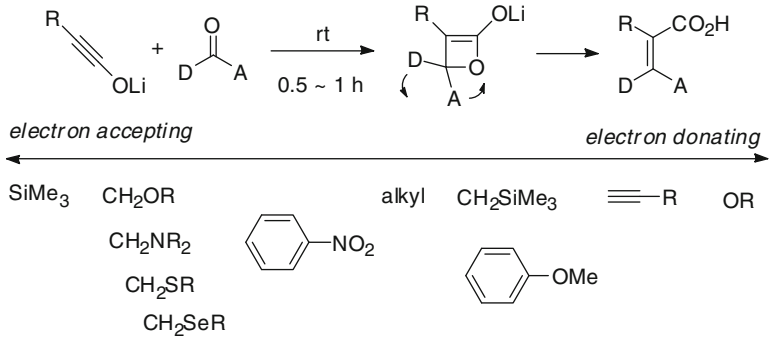


Fig. 54 General scheme for torquoselective olefination

cyclobutenes. Recently, the significance of torquoselectivity has been considered for the stereoselective Nazarov reaction. In the ring opening of oxetenes (β-lactone enolates), much higher torquoselectivity is achieved than that in the case of cyclobutenes and that leads to highly stereoselective olefination. Torquoselective olefination is mechanistically quite different from conventional methods such as the Wittig reaction and can achieve high efficiency and stereoselectivity in the olefination of various kinds of carbonyl compounds, providing alkenes that are otherwise difficult to prepare. The stereoselectivity can be estimated theoretically by a consideration of the electronic properties of the substituents. At present, the order of electron-donating and accepting properties is apparent as shown in Fig. 54. Further studies will possibly make it clearer. This methodology will hopefully be used in various types of organic syntheses in the near future.

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Top Curr Chem (2012) 327: 33–58
DOI: 10.1007/128_2012_315

Published online: 6 March 2012

Stereoselective Synthesis of *Z*-Alkenes

Woon-Yew Siau, Yao Zhang, and Yu Zhao

Abstract This chapter offers a general review of the evolvement of methods for the stereoselective synthesis of *Z*-alkenes**,** with a focus on the development of catalytic systems towards this goal in recent years.

Keywords Cross coupling · Lindlar reduction · Olefin metathesis · Olefination · *Z*-Alkene

Contents

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1 Introduction

Alkenes are ubiquitous in biologically active entities and serve as versatile starting materials for a large number of chemical transformations [1–6]. The stereochemistry of the alkenes, namely the *E*- or *Z*-isomeric form, not only determines the property of the molecules but also in most cases alters the stereochemical outcome of the reactions utilizing alkenes as starting materials. Stereoselective access to either isomer, therefore, is a key component of alkene synthesis. In general, methods for highly selective access to *Z*-alkenes are less established than those for the *E*-isomers. One of the reasons is thermodynamic control that favors the lower-in-energy *E*-alkenes.

Since a wide variety of methods are suitable for *Z*-alkene synthesis (albeit not always general methods), including the most important reactions in organic synthesis such as Wittig olefination, cross coupling, and olefin metathesis, it is the intention of the authors to illustrate the evolution of methods for *Z*-alkene synthesis through representative examples, with a focus on the development of catalytic methods in recent years.

2 Olefination Reactions: from Carbonyls to Alkenes

2.1 Wittig Reaction

The Wittig reaction has proved to be one of the most important methods for alkene synthesis and has found much use in natural product synthesis [7–10]. In this transformation, the carbonyl compound reacts with a phosphorus ylide (prepared from a triaryl- or trialkylphosphine and an alkyl halide followed by deprotonation with a suitable base) to yield the alkene product with concomitant generation of phosphine oxide as the side product. The stereoselectivity of Wittig reaction is influenced by many factors including type of ylides, type of carbonyl compounds, nature of solvent, and even the counterion for the ylide formation. In general, good to high *Z*-selectivity (typically ~9:1) can be expected when "nonstabilized" (alkyl substituted) ylides react with aldehydes under salt-free conditions in a dipolar aprotic solvent. One impressive example reported in recent years, in which two partners with a complex structure were coupled in a highly *Z*-selective fashion, is

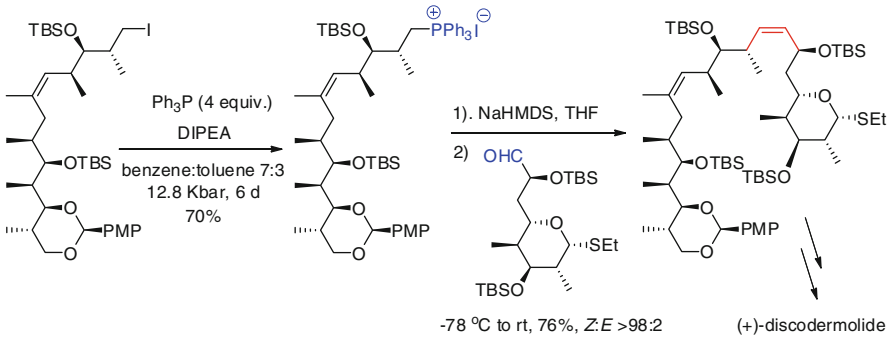

Fig. 1 Wittig olefination coupled two pieces with a complex structure to yield *Z*-alkene

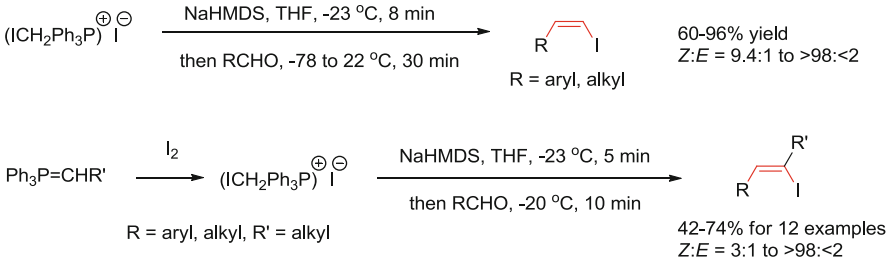

Fig. 2 Wittig reaction for the preparation of *Z*-alkenyl iodides

shown in Fig. 1 [11]. The alkene product was then transformed to the natural product named (+)-discodermolide, a potent inhibitor of tumor cell growth.

The utilization of the Wittig reaction to prepare functionalized alkenes such as *Z*-vinyl halides has also been demonstrated since the early 1990s (Fig. 2) [12]. The iodoalkyl phosphonium salt is deprotonated with sodium hexamethyldisilazane to yield the ylide that reacts with aldehydes to generate the *Z*-alkenyl halides in good to excellent selectivity. Not only disubstituted *Z*-alkenyl halides, but also trisubstituted ones can be prepared using this method, albeit with moderate chemical yields [13]. These products are useful synthons in organic synthesis, especially in cross coupling reactions.

Much effort was expended on improving the *Z*-selectivity of Wittig reaction for a wider range of substrates by modifying the nature of the ylide or the carbonyl compounds. Very recently, the Tian group reported Wittig olefination utilizing sulfonyl imines as the substrate that provides a wide range of alkenes including conjugated dienes exclusively as the *Z*-isomer (Fig. 3) [14]. Traditional Wittig olefination only provides these products as a mixture of *E*- and *Z*-alkenes. It is important to note that the substituent on the sulfonyl imines has a significant impact on the stereoselectivity of the process. By tuning the steric and electronic properties of the substituents, either *E*- or *Z*-alkenes can be accessed exclusively. Even though

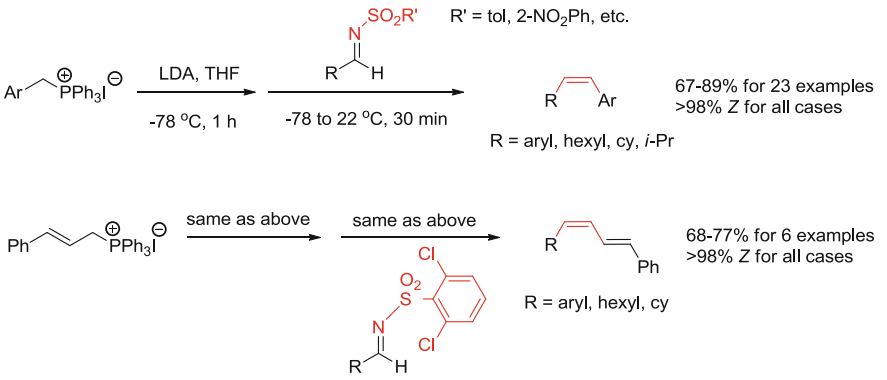

Fig. 3 Highly *Z*-selective Wittig reaction of sulfonyl imines

this method is not very appealing in terms of atom economy, it represents an exciting improvement of *Z*-selective Wittig olefination.

While being widely used for alkene synthesis, it is noteworthy that, as a stoichiometric transformation, Wittig reaction generates extensive waste due to the high mass of phosphine oxide side product which is not always easily separable from the desired product. While Wittig reaction catalytic in phosphine is merging [15], the establishment of fully compatible catalytic olefination processes is yet to be seen.

2.2 *Still–Gennari Modification of the Horner–Wadsworth–Emmons Olefination*

As an important modification of Wittig reaction, the Horner–Wadsworth–Emmons (HWE) olefination gives rise to α,β-unsaturated ketones and esters with significant advantages over Wittig reaction including easier reagent preparation, wider substrate scope (especially as hindered ketones undergo HWE but not Wittig reaction), as well as much more straightforward separation of the dialkyl phosphate side product (since it is water soluble) from the alkenes of interest [16]. However, HWE reaction proceeds in an exclusively *E*-selective fashion.

In 1983, Still and Gennari introduced the first general way to prepare *Z*-alkenes by coupling electrophilic bis(trifluoroalkyl) phosphonoesters in the presence of strong bases with aldehydes (Fig. 4) [17]. The bis(trifluoroethyl)phosphonoesters are easily prepared from the commercially available trialkylphosphonoesters and trifluoroethanol. Both 1,2-disubstituted and trisubstituted *Z*-alkenes can be accessed using this method, but the products are limited to α,β-unsaturated ketones, esters, or cyanides, since the electrophilic phosphonate reagent requires an electron-withdrawing group at

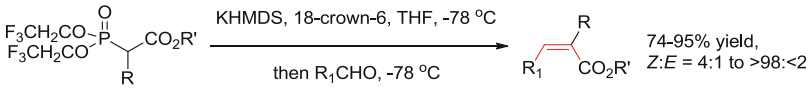

Fig. 4 Still–Gennari modification of HWE olefination leads to *Z*-α,β-unsaturated ketones/esters

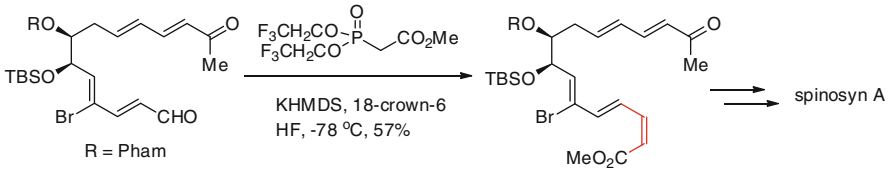

Fig. 5 Still–Gennari modified HWE olefination for polyene synthesis

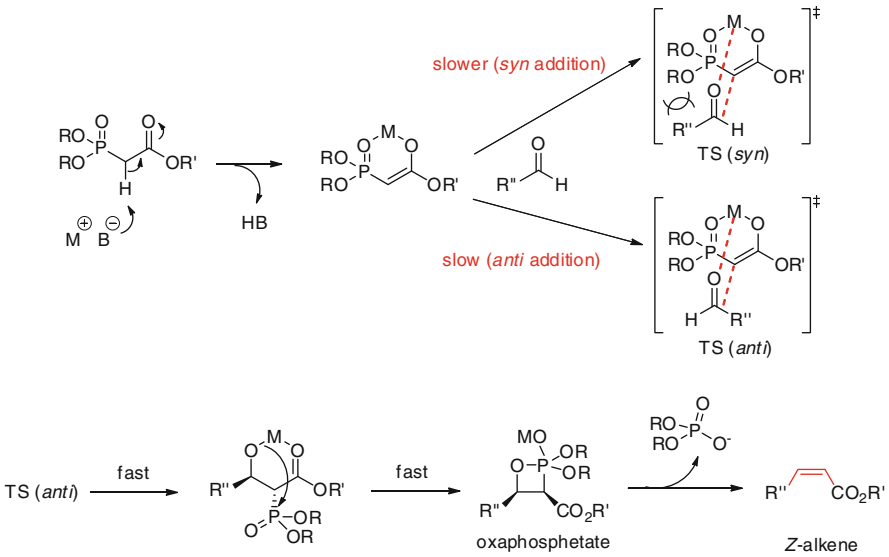

Fig. 6 Rationale for Z-selectivity in Still–Gennari modification of HWE olefination

its α-position to stabilize the carbanion. Usually 18-crown-6 is used as an additive because a non-coordinating metal cation is necessary for the reaction to work.

Since its original report, the Still–Gennari modified HWE olefination has been widely used in natural product synthesis to access *Z*-alkenes [18]. One example from the Roush group is shown in Fig. 5, where the olefination reaction was used to provide the conjugated polyene precursor for their key one-pot tandem intramolecular Diels–Alder reaction and vinylogous Baylis–Hillman cyclization [19].

Although the mechanism for the HWE olefination is not fully understood, the rationale for the reverse selectivity of Still–Gennari modification merits further discussion [20]. As shown in Fig. 6, it is believed that the steps for the HWE

olefination are reversible (or quasi-reversible) so that the *E*-alkene that is lower in energy is selectively formed in essentially all cases. In the Still–Gennari modified version, however, due to the electron-withdrawing effect of the two trifluoroalkoxy groups on the phosphorus, the formation of the oxaphosphetane from the chelated adduct is much more favored than in the regular HWE reaction, rendering a faster elimination step than the initial addition. Since the whole process becomes irreversible, the kinetic selectivity in the initial addition step that favors *anti*-addition leading to *Z*-alkene product based on steric interaction is maintained.

3 Cross Coupling Reactions

3.1 Pd- or Ni-Catalyzed Cross Coupling: Complexity Generation from Z-Alkenyl Halides or Alkenylmetals

Pd- or Ni-catalyzed cross coupling reactions of alkenyl halides or alkenylmetal species have established themselves as powerful tools for accessing either *E*- or *Z*-alkenes [21]. The cross coupling step is stereospecific in most cases and results in the retention of the stereochemistry of the starting alkenyl halides or alkenylmetal species. The control of the alkene isomer, therefore, has to be established before the cross coupling step, which is invaluable as the complexity generation step in organic synthesis. Instead of presenting a general review of this area of research that is beyond the scope of this chapter, two representative examples of Suzuki and Negishi coupling to access *Z*-alkenes from *Z*-alkenyl iodides or *Z*-alkenyl boranes are shown in Figs. 7 and 8.

The Molander group reported a formal total synthesis of oximidine II, in which an intramolecular Suzuki cross coupling between an *E*-alkenyl potassium trifluoroborate and a *Z*,*Z*-dienyl bromide constructed the highly strained 12-membered macrolactone core of the natural product (Fig. 7) [22]. Importantly, the stereochemistry of the starting partners was conserved to deliver the *E*,*Z*,*Z*-conjugated triene in the natural product.

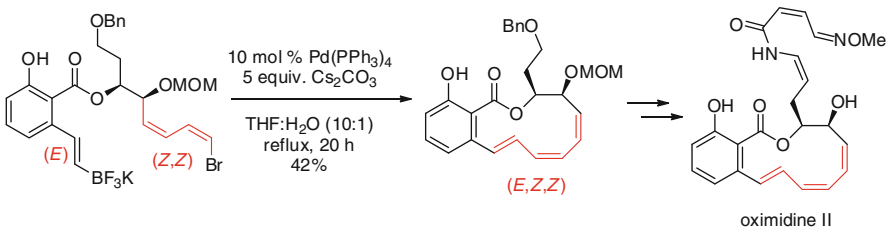

Fig. 7 Suzuki coupling for macrocyclization to install *E*,*Z*,*Z*-triene

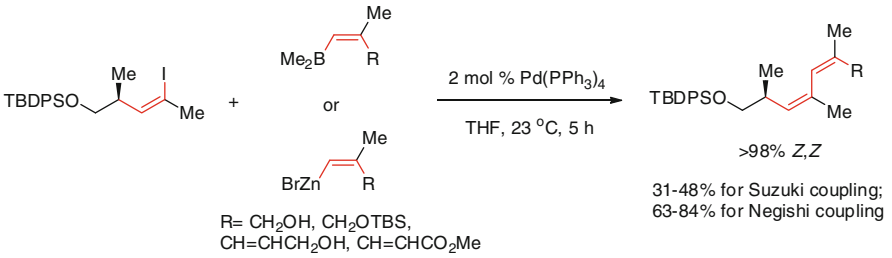

Fig. 8 Cross coupling of *Z*-alkenyl halide leads to *Z*-alkenes

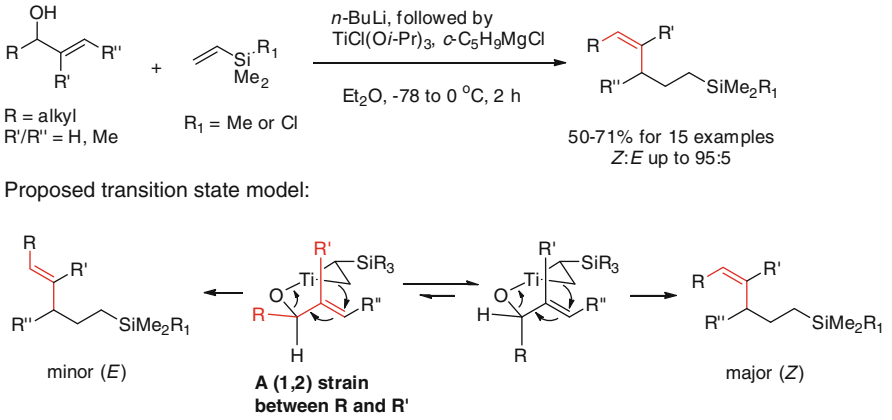

Fig. 9 Cross coupling of allylic alcohols and vinyl silanes mediated by Ti complex

Negishi and co-workers compared Negishi coupling and Suzuki coupling for the preparation of conjugated dienes (Fig. 8) [23]. In particular, *Z*,*Z*-dienes are constructed in high purity starting from *Z*-alkenyl iodides and either *Z*-alkenyl borane or zinc species. The Negishi coupling, however, was found to be more efficient and to deliver the products in higher chemical yields.

3.2 Other Cross Coupling Reactions

The Micalizio group reported an interesting cross coupling of allylic alcohols and vinyl silanes mediated by a titanium complex (Fig. 9) [24]. Good *Z*-selectivity (95% in most cases) was obtained for a wide range of substrates. The titanium complex is proposed to coordinate to both substrates and join them together in a closed transition state. As shown in the proposed model, the minimization of A-1,2 strain is believed to be the source of *Z*-selectivity of the system.

4 Transformation of Alkynes to *Z*-Alkenes

4.1 Partial Hydrogenation with Lindlar's Catalyst and Beyond

4.1.1 Lindlar Reduction

The partial hydrogenation of alkynes using Lindlar's catalyst is widely utilized for accessing disubstituted *Z*-alkenes. In contrast to Pd on activated carbon which readily catalyzes the hydrogenation of alkynes and alkenes to the corresponding alkanes, in Lindlar catalyst the Pd catalyst (5–10 wt%) is deposited on $CaCO_3$ and further "poisoned" with a lead co-catalyst (lead acetate or lead oxide) and quinoline in order to decrease its catalytic activity so that the reaction can be intercepted at the alkene stage. The mechanism is believed to be similar to the heterogeneous Pd- or Pt-catalyzed hydrogenation of alkenes. Due to the nature of heterogeneous catalysts, H_2 is bound to the surface of the catalyst and *Z*-configured alkenes could be generated exclusively.

Ever since its introduction by Hebert Lindlar [25], Lindlar reduction has found extensive application in organic synthesis. One representative example from the Ghosh group, where Lindlar reduction was used at a late stage of the total synthesis of the potent antitumor macrolide (−)-laulimalide, is shown in Fig. 10 [26]. Thus, Yamaguchi macrolactonization of the hydroxy alkynoic acid followed by Lindlar reduction yielded the *Z*-α,β-unsaturated ester in high efficiency that is only a few deprotection steps away from the natural product. It is important to point out that in their earlier attempts, when the corresponding *Z*-α,β-unsaturated acid was first prepared and used for the Yamaguchi macrolactonization step, significant isomerization of *Z*-alkene to the *E*-isomer was observed. It was postulated that this undesired isomerization was the result of the reversible Michael addition of DMAP (instead of 1,2-addition for Yamaguchi macrolactonization) to the mixed anhydride intermediate of this macrocyclization step. The fact that Lindlar reduction can be carried out efficiently at such a late stage was key for the success of the synthesis.

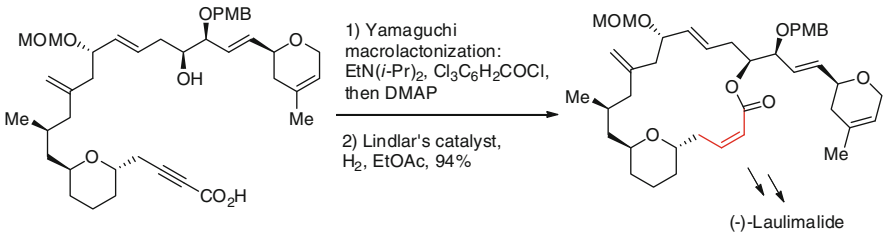

Fig. 10 Lindlar reduction of macrocycles in natural product total synthesis

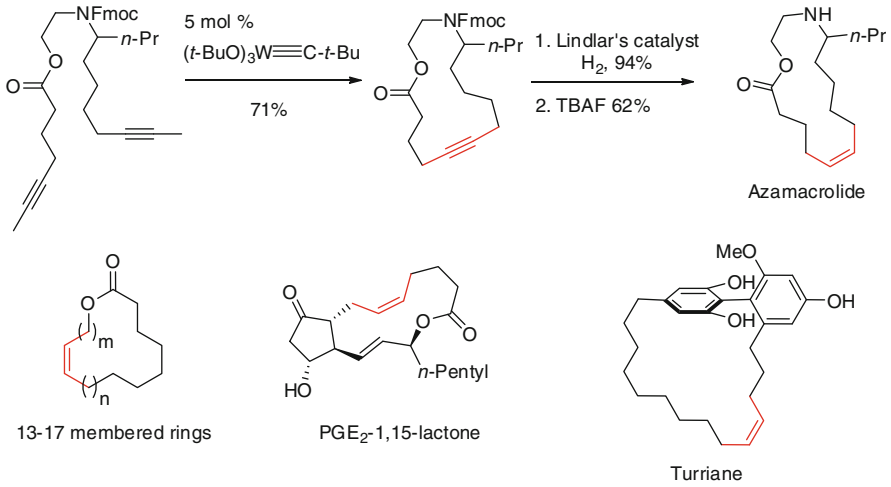

Fig. 11 RCAM/Lindlar reduction for the synthesis of macrocyclic *Z*-alkenes

In an effort to address the problem of lack of stereo-control for the alkene geometry in ring closing olefin metathesis macrocyclization, the Fürstner group introduced ring-closing alkyne metathesis (RCAM) followed by Lindlar reduction as a powerful tool for accessing *Z*-macrocycloalkenes stereoselectively [27]. The Schrock tungsten carbyne complex [(*t*-BuO)$_3$W≡C-*t*-Bu] [28] or the molybdenum chloride species formed in situ from [Mo{N(*t*-Bu)(Ar)}$_3$] and CH_2Cl_2 [29] were found to be efficient precatalysts for these processes. Unlike alkene metathesis, where terminal diene serves effectively as the substrate, the substrate for alkyne metathesis has to be internal alkynes. In the past decade the Fürstner group has used this method to prepare a wide range of macrocyclic natural products, representative examples of which are shown in Fig. 11 [30]. The *Z*-alkenes highlighted in red were all prepared using the RCAM/Lindlar reduction sequence.

In spite of the great synthetic utility, Lindlar's catalyst suffers from several significant drawbacks. As a heterogeneous catalyst, the performance of Lindlar's catalyst may vary from batch to batch. While the use of not enough catalyst results in incomplete conversion, adding excess catalyst very often leads to over reduction to the saturated alkanes. This is a serious problem because it is extremely difficult to convert the alkane back to the desired alkene product. As a matter of fact, addition of Lindlar's catalyst in portions while closely monitoring the reaction conversion is a common practice, which makes this procedure tedious and impractical. In addition, the use of toxic lead co-catalyst poses problems in terms of environmental and safety issues.

Much effort was expended to improve the performance of the catalytic system, including using Pd on pumice [31] as well as different amine co-catalysts to deactivate Pd such as ethylenediamine [32]. A new general catalytic system superior to the original Lindlar's catalyst has not been discovered so far.

4.1.2 Other Metals for Partial Hydrogenation of Alkynes to *Z*-Alkenes

In 1973, Brown and Ahuja introduced an interesting alternative method to Lindlar reduction that uses P-2 nickel in the presence of ethylenediamine for the partial hydrogenation of alkynes to *Z*-alkenes [33]. The nickel catalyst can be generated in situ through the reduction of nickel acetate by $NaBH_4$, which makes it straightforward to control the exact catalyst loading for the reaction.

In their efforts to prepare a [D_4]-labeled F_{4t}-neuroprostane, the Galano group carried out partial reduction of the skipped diyne substrate in order to access the *Z*,*Z*,*Z*-triene moiety of the final product (Fig. 12) [34]. While Lindlar's catalyst provided a mixture of mono-reduction of the less hindered alkyne (with the ethyl substituent), the desired triene as well as over-reduced diene product, P-2 nickel yielded a much cleaner conversion to the desired product with 98% purity. The product was then transformed into the target molecule by a sequence of TBAF deprotection of the TBS ether and saponification.

In 1995, Sato and co-workers reported that low-valent titanium alkoxide prepared from Ti(O*i*-Pr)$_4$ and *i*-PrMgCl (1:2) can readily incorporate alkynes to give a titanacyclopropene complex, hydrolysis of which then leads to *Z*-alkenes with high efficiency and excellent stereoselectivity (Fig. 13) [35].

Very recently, the groups of Bergman and Arnold reported that a d^2 niobium–imido complex catalyzes an efficient and selective partial hydrogenation of 1-phenyl-1-propyne to *Z*-β-methylstyrene under H_2/CO mixtures (Fig. 14) [36]. An Nb(V) metallacyclopropene complex similar to the previous Ti system was proposed, which was followed by σ-bond metathesis with H_2 and subsequent reductive elimination to yield the *Z*-alkene. An excess of CO is required not only for catalyst stability but also for achieving catalyst turnover by replacing the product from the Nb complex. However, only one substrate was included in this report.

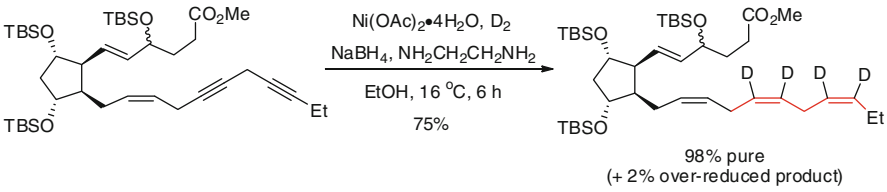

Fig. 12 P-2 Nickel-catalyzed hydrogenation of skipped diyne

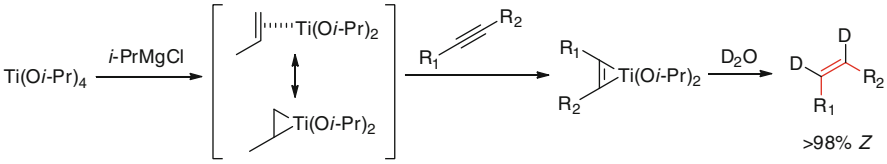

Fig. 13 *Z*-Alkenes from reaction of low-valent Ti alkoxide with alkynes followed by hydrolysis

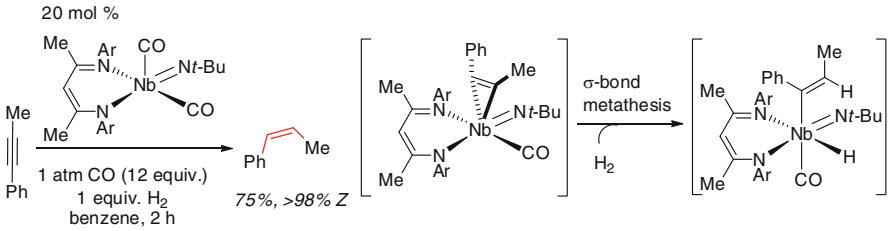

Fig. 14 Nb-imido complex catalyzed partial hydrogenation of alkyne

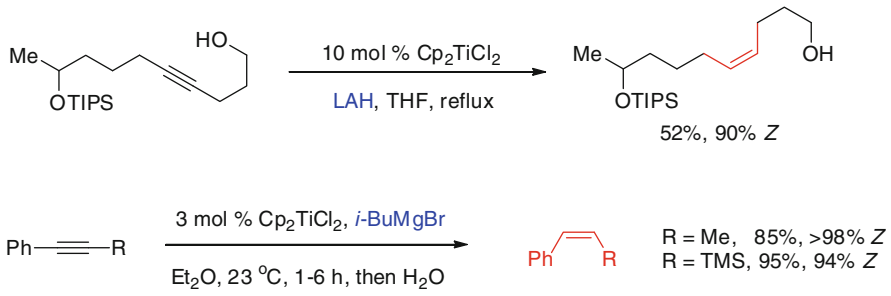

Fig. 15 Ti-catalyzed hydroalumination and hydromagnesation of internal alkynes

4.2 Hydrometalation of Alkynes to Z-Alkenes

Hydrometalation of alkynes is one of the most direct and powerful synthetic tools for the formation of alkenyl metal species, which could be simply hydrolyzed to yield the corresponding alkenes or readily utilized as building blocks for further transformations such as cross coupling and electrophilic substitution reactions.

4.2.1 *Syn*-Hydrometalation of Internal Alkynes to Disubstituted *Z*-Alkenes

In general, non-catalyzed hydrometalation reactions including hydroboration proceed in a *syn*-fashion. When internal alkynes undergo hydrometalation followed by hydrolysis, disubstituted *Z*-alkenes can be accessed selectively; representative examples of Ti-catalyzed hydroalumination and hydromagnesation are demonstrated in Fig. 15. In the first example, it was noted that the hydroalumination reaction in the absence of the Ti catalyst led to the *E*-isomer [37]. In the second example, it was shown that, in addition to hydrolysis, the alkenylmagnesium intermediate could undergo addition to aldehydes and alkyl halides to yield trisubstituted alkene products in high stereoselectivity [38].

4.2.2 Hydrometalation of Terminal Alkynes to Access *Z*-Alkenes

The Brown group developed a multi-step procedure including *syn*-hydroboration of terminal alkynes and *trans*-bromination followed by *trans*-elimination to access *Z*-alkenyl bromides (Fig. 16) [39].

Transition metal catalyzed hydroboration may alter the stereoselectivity of hydroboration of terminal alkynes. Miyaura and co-workers reported a rhodium-catalyzed *trans*-hydroboration of terminal alkynes (Fig. 17) [40]. Deuterium labeling studies strongly suggested that the reaction proceeded through a vinylidene intermediate, which explained the formation of *Z*-alkene products.

In contrast to hydroboration, hydrosilylation and hydrostannation generally do not take place in the absence of a Lewis acid catalyst or a radical initiator. Two representative examples of such reaction types are illustrated in Fig. 18 [41, 42]. These reactions are postulated to proceed through the *trans*-attack of hydrosilane/hydrostannane on the Lewis acid-activated alkyne followed by transmetallation to produce the *Z*-alkenyl silane/stannane products and regenerate the catalyst.

Other *trans*-hydrometalation of alkynes includes the use of a combination of $InCl_3$ and DIBAL to produce alkenyl indium species [43], and a Lewis acid catalyzed hydrogermylation of terminal/internal alkynes (Fig. 19) [44]. In both cases, *trans*-hydrometalation was believed to account for the stereoselectivity of the reactions.

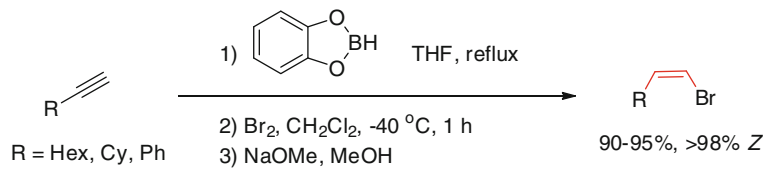

Fig. 16 Multiple-step procedure to access *Z*-alkenyl bromide based on hydroboration

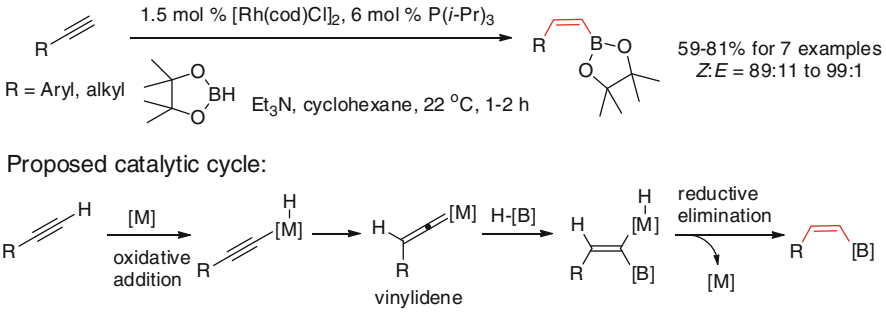

Fig. 17 Rh-catalyzed *trans*-hydroboration of terminal alkynes

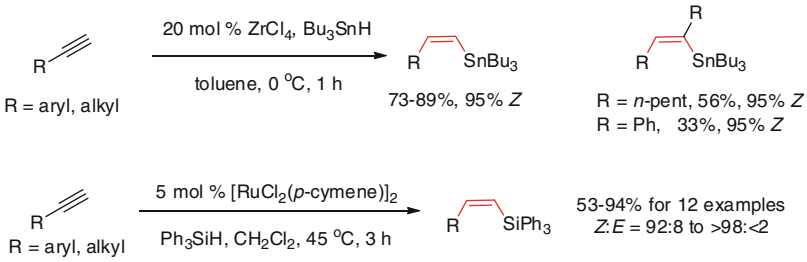

Fig. 18 *trans*-Hydrosilylation and hydrostannation of terminal alkynes

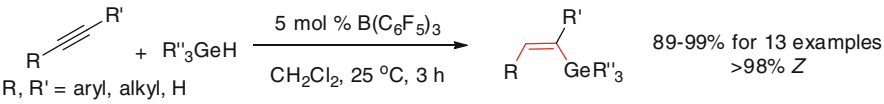

Fig. 19 *trans*-Hydrogermylation of alkynes

5 *Z*-Selective Olefin Metathesis

In spite of impressive advances in the development of catalytic olefin metathesis reactions [45], lack of stereoselective access to *Z*-alkenes represented a significant shortcoming in olefin metathesis for decades. With the exception of ring-closing metathesis (RCM) to access small-sized rings where the formation of *E*-isomer causes too much strain in the molecule, most metathesis reactions afford either mainly *E*-alkenes or a mixture of the two isomers in low ratios. Only in a few cases, especially when one of the starting alkenes bears a sp-hybridized substituent, was moderate to good *Z*-selectivity obtained for metathesis reactions (see Section 5.1). Very recently, through the development of new Mo- or W-alkylidene complexes (see Section 5.2) and Ru-carbene complexes (see Section 5.3), a general access to *Z*-alkenes in high to excellent stereoselectivities through olefin metathesis was finally realized.

5.1 Early Examples

As one of the earliest demonstrations of the synthetic utility of selective ring-opening cross-metathesis (ROCM) reactions, Snapper and co-workers reported the ROCM of substituted cyclobutene and terminal olefins to yield 1,5-diene products catalyzed by Grubbs' first generation catalyst in 1995 (Fig. 20) [46]. Although the selectivity was only moderate (generally 2:1 *Z*:*E* for six examples reported), the bias towards the formation of *Z*-alkene represents a rare example. A model was proposed to account for the selectivity, where steric interactions between the substrate and the phosphine ligand are minimized [47].

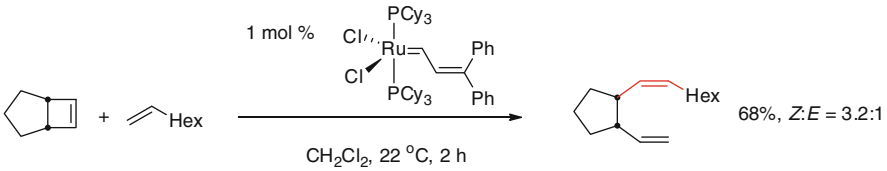

Fig. 20 ROCM of substituted cyclobutene with terminal alkenes

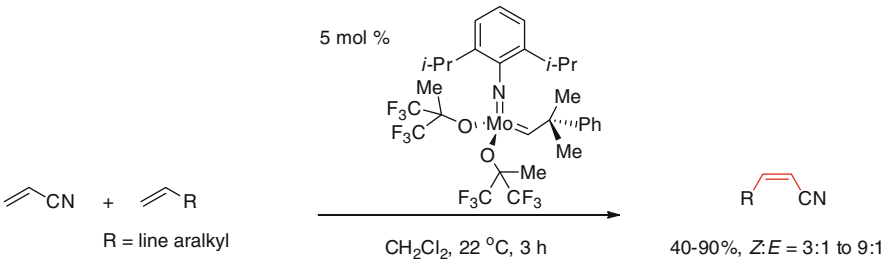

Fig. 21 *Z*-Selective cross metathesis of acrylonitrile with terminal olefins

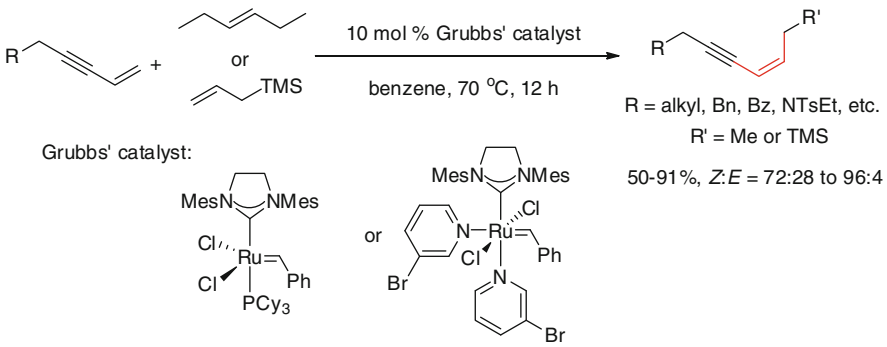

Fig. 22 *Z*-Selective cross metathesis employing conjugated enynes

In the same year the Crowe group reported the first example of *Z*-selective cross metathesis of acrylonitrile and various terminal olefins catalyzed by Schrock catalyst shown in Fig. 21 [48]. Acrylonitrile was required to achieve moderate to good *Z*-selectivities. A model that minimizes steric interaction between imido ligand of the catalyst and the substituent on the alkene was proposed to account for the *Z*-selectivity. In 2001 the Blechert group reported that second-generation Hoveyda–Grubbs catalyst promoted similar reactions with essentially the same level of *Z*-selectivity (typically 4:1 *Z*:*E*) [49].

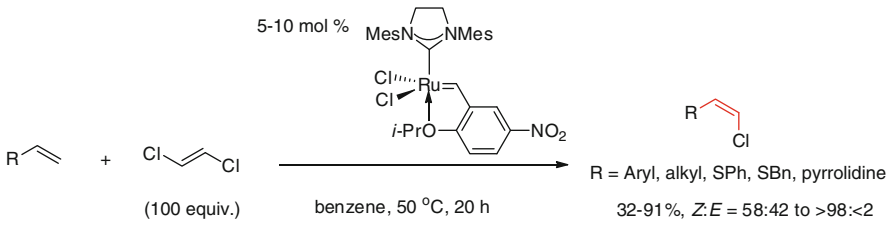

Fig. 23 *Z*-Chloroalkenes from cross metathesis

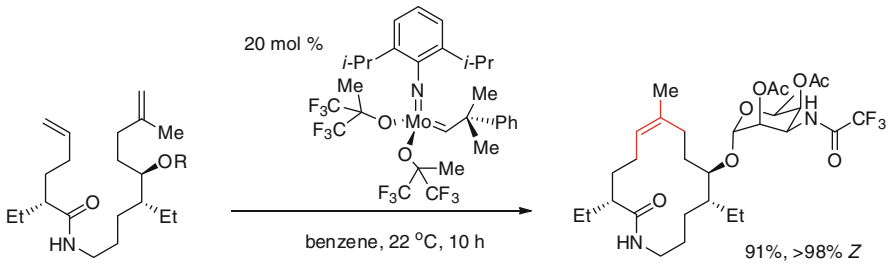

Fig. 24 *Z*-Selective RCM macrocyclization as a late-stage key step in total synthesis

Z-Selective cross metathesis employing conjugated enynes as one of the cross partners was developed by the Chang group (Fig. 22) and the Lee group, among others [50–52]. Over 20 examples were reported in the original paper, but the *Z*-selectivity varied from 72:28 to 96:4. Second-generation Grubbs' catalyst or the more reactive pyridine supported complex was used for these reactions.

An interesting preparation of *Z*-alkenyl chlorides by cross metathesis was reported by the Grela group (Fig. 23) [53]. NO_2-substituted Hoveyda–Grubbs second-generation catalyst promoted the cross metathesis of 1,2-dichloroethane with a few highly functionalized terminal alkenes to yield the products with up to >98% *Z*-selectivity. A large excess of 1,2-dichloroethane was required in this reaction. The rationale for this intriguing *Z*-selectivity was not provided.

As one of the earliest applications of RCM for macrocyclization in natural product synthesis, the Hoveyda group reported in 1995 that Schrock catalyst catalyzed *Z*-selective formation of the macrocycle in Fig. 24 as a single alkene stereoisomer, which is a late stage intermediate for the total synthesis of Fluvirucin B [54]. While the conformational control of the substrate was believed to be crucial for the selectivity, recent studies showed that catalyst control also played a key role in the reaction outcome, as Ru-catalyzed RCM of a very similar substrate yielded a 1:1 mixture of *Z*:*E* isomers [55].

5.2 *Recent Development of Mo- and W-Alkylidene Monoaryloxide Pyrrolide Complexes for Highly Z-Selective Olefin Metathesis*

In the past few years the groups of Schrock at MIT and Hoveyda at Boston College introduced a new type of Mo-alkylidene MonoAryloxide Pyrrolide (MAP) complexes as highly reactive and enantioselective olefin metathesis catalysts [56, 57]. These stereogenic-at-metal complexes supported by non-chelating ligands turned out to be fascinating catalysts for *Z*-selective olefin metathesis reactions with the level of *Z*-selectivities that was completely out of reach before.

5.2.1 ROCM and Ring-Opening Metathesis Polymerization

The first report was ROCM of oxabicycles with styrene (one example of allyl TBS ether was also reported) to yield the trisubstituted tetrahydropyran products in high enantioselectivities, and, more importantly, up to >98% *Z*-selectivity (Fig. 25) [58]. It is noteworthy that when a closely related catalyst supported by a more bulky 2,6-diisopropylphenyl imido group (instead of the smaller adamantyl imido as in the catalyst shown) was used, no product was obtained.

An intriguing model for *Z*-selectivity was proposed: the formation of a trigonal bipyramidal metallacyclobutane intermediate and the size difference of the imido and the aryloxide ligands are considered to be the key factors (Fig. 26). The combination of a sterically demanding but freely rotating (around the Mo–O bond) aryloxide and a sufficiently smaller imido group favors reaction through the *syn* alkylidene isomer and the approach of the incoming alkene with the substituents directed towards the imido ligand to form an all-*cis* metallacyclobutane. Cycloreversion then produces *Z*-alkene products with regeneration of the *syn* alkylidene.

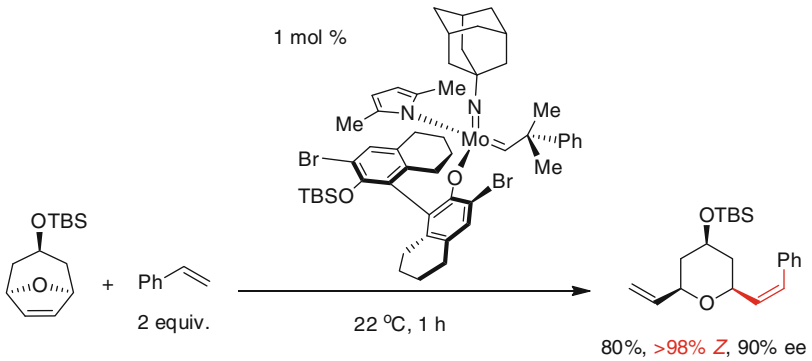

Fig. 25 Highly enantioselective and *Z*-selective ROCM of oxabicycle with styrene

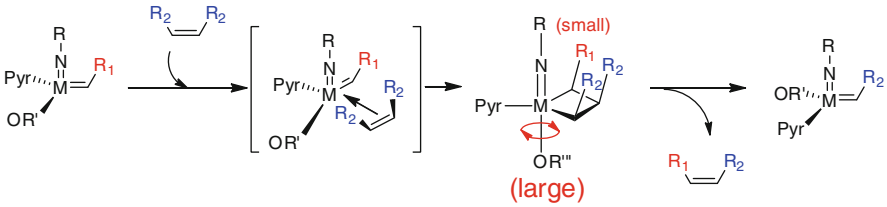

Fig. 26 Proposed model for *Z*-selectivity

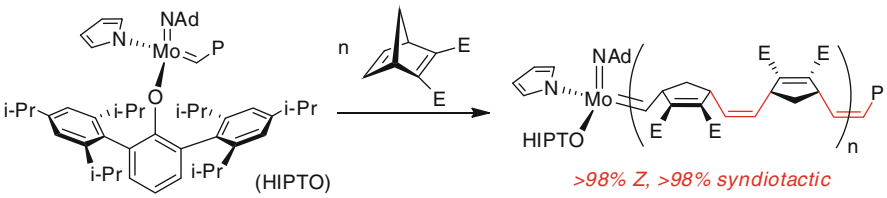

Fig. 27 ROMP leads to *cis*- and *syndiotactic* polymer structures

Ring-Opening Metathesis Polymerization (ROMP) of norbornadiene derivatives catalyzed by the new Mo-MAP catalyst was carried out successfully by Schrock and co-workers (Fig. 27) [59]. Polymers with a *cis*-, *syndiotactic* configuration, which was not known in pure form before, can be accessed in this way. The same model was believed to account for the *Z*-selectivity of the reactions, for which the Mo-catalyst bearing an even more sterically bulky hexaisopropyltriphenoxide (HIPTO) ligand turned out to be optimal. Another intriguing feature of this system is the control of the tacticity by the stereogenic metal center. The same principle was also extended to the preparation of *cis*-, *syndiotactic* ROMP polymers containing alternating enantiomers when racemic norbornadiene derivatives were used for the polymerization [60].

5.2.2 Cross Metathesis Reactions Catalyzed by Mo- or W-MAP Complexes

Extension of the previous systems to general cross metathesis had another hurdle to overcome: isomerization of the kinetically formed *Z*-alkene to the *E*-alkene that is lower in energy. This is due to the fact that there is no release of strain in the substrate to manipulate as in ROCM and the reactions are under thermodynamic control.

The Schrock lab focused on the development of new catalysts to address the *Z*-selectivity for a simplified cross metathesis: homocoupling of terminal alkenes (Fig. 28) [61, 62]. While various Mo-MAP catalysts including the optimal ones for the previous systems failed to provide homocoupled internal olefins in high *Z*-selectivity, it was discovered that the less reactive W-based MAP complexes **A** and **B** supported by the sterically bulky HIPTO or the 3,3′-bismesityl-aryloxide

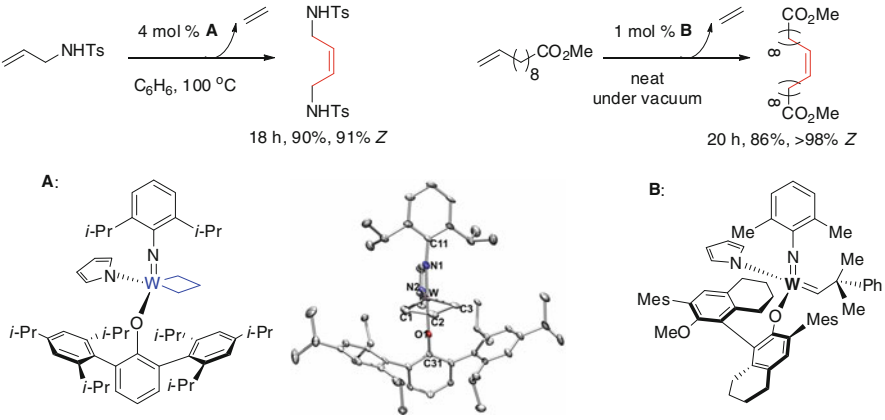

Fig. 28 Z-Selective homocoupling of terminal alkenes catalyzed by W-MAP complexes

can catalyze the homocoupling reactions with good to excellent levels of *Z*-selectivity. The isomerization pathway was minimized under the reaction conditions, resulting in a better conservation of the kinetic *Z*-selectivity. Metallacyclobutane **A** can be used efficiently as a catalyst for this reaction; the corresponding neophylidene precatalyst can also be generated in situ and used for the reaction with the same efficiency. The X-ray structure of **A** provided strong support for the model of *Z*-selectivity proposed earlier: in this trigonal bipyramidal structure, the imido group and the sterically demanding HIPTO ligand reside at the axial positions; the bottom face of the metallacyclobutane is much less accessible due to steric hindrance of the aryloxide. As a matter of fact, space filling model of **A** showed that the protons on the lower face of the metallacycle are in close contact with the protons on the isopropyl group from the aryloxide ligand.

The Hoveyda group worked out an elegant cross metathesis of terminal alkenes with vinyl ethers or allylic amides [63]. Functionalized vinyl ethers and allylic amides can be directly accessed with unprecedented *Z*-selectivity, which have been applied to the total synthesis of two highly valuable natural products including an anti-oxidant plasmalogen phospholipid (Fig. 29) and a potent immunostimulant KRN7000.

As shown by the sequence in Fig. 29, cross metathesis between the vinyl ether and an aliphatic alkene proceeded in a highly *Z*-selective fashion to provide, after removal of the silyl group, the propargyl alkenyl ether in high chemical yield and in a stereoisomerically pure form. Cu-catalyzed site- and enantioselective dihydroboration of the alkyne, another methodology developed in the Hoveyda group [64], then furnished the glycerol derivative in high enantioselectivity as a single *Z*-isomer, which could be converted to the desired product C18 (plasm)-16:0 (PC) in four steps [65].

The use of vinyl ethers (usually in excess) is mechanistically intriguing. The excess vinyl ether readily reacts with the reactive Mo-methylidene complex generated after the productive metathesis step and circumvents diminution in

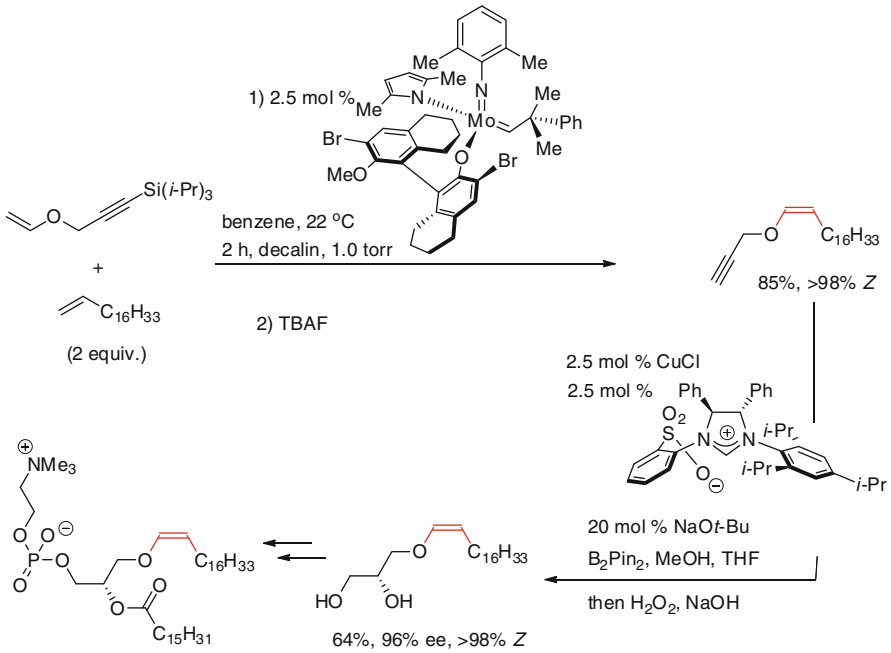

Fig. 29 *Z*-Selective cross metathesis of vinyl ethers for synthesis of plasmalogen phospholipid

Z-selectivity of the product through equilibration of the isomers that would be facile if Mo-methylidene is allowed to accumulate. The more stable alkoxy-substituted alkylidene does not undergo homocoupling due to an electronic mismatch, but can efficiently undergo productive cross metathesis with terminal alkenes; in this way, a selective cross metathesis can be achieved.

5.2.3 *Z*-Selective RCM Catalyzed by W-MAP Complexes

RCM has been extensively utilized to access macrocyclic natural products, the stereoselectivity of which, however, represented a significant limitation of this methodology. In most cases the low energy difference between the alkene isomers resulted in a mixture of two products in low ratios. The reported chemical syntheses of the anti-cancer drug epothilones from a few research groups, for example, all relied on RCM as a key step and the macrocyclic intermediates were only generated in a *Z*:*E* ratio ranging from 1:2 to <2:1 [66, 67] (see [30] for the alternative alkyne metathesis/Lindlar reduction sequence by the Fürstner group).

Very recently the Hoveyda group extended the application of W-MAP catalysts to *Z*-selective RCM macrocyclization (Fig. 30) [68]. In contrast to previous systems that delivered the desired product in low *Z*:*E* ratios, the desired *Z*-isomer was obtained in a selectivity up to 97% and with good to high chemical yield.

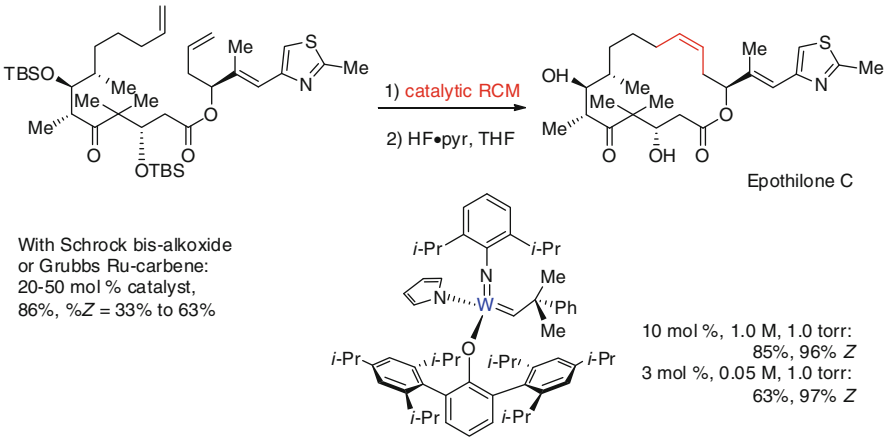

Fig. 30 *Z*-Selective RCM for the synthesis of Epothilone C

It is believed that the W-based catalyst (less reactive than the Mo analog) possesses the appropriate reactivity level so that it readily catalyzes the *Z*-selective cyclization of the terminal diene substrate but fails to promote, to a significant extent, the ring-opening/ring-closing pathway that can cause alkene isomerization. In this paper the authors also reported the use of the same catalytic system for the highly *Z*-selective synthesis of the 15-membered ring moiety of nakadomarin A (another anti-cancer agent), as well as a highly flexible 16-membered lactone. It is also noted that numerous other total syntheses of biologically active macrocyclic molecules may similarly benefit from the reported protocols.

One drawback of the Schrock type olefin metathesis catalysts that limited their synthetic utility is their high sensitivity to air (oxygen) or moisture. The W-catalyst used in this study, however, turned out to be sufficiently stable to be handled in air under up to 80% humidity. This practical advantage will certainly facilitate its wide use in organic synthesis.

5.3 *Recent Development of Ru–Carbene Complexes for Highly Z-Selective Olefin Metathesis*

Earlier this year, the Grubbs group reported the preparation of the Ru-based catalyst with a chelating *N*-heterocyclic carbene (NHC) ligand that catalyzes highly *Z*-selective olefin metathesis (Fig. 31) [69, 70]. This catalytic system provided similar levels of efficiency and selectivity to the W-alkylidene complexes for homocoupling reactions. The reason for the *Z*-selectivity is not clear at this point. Extension of the substrate scope of this catalytic system is expected.

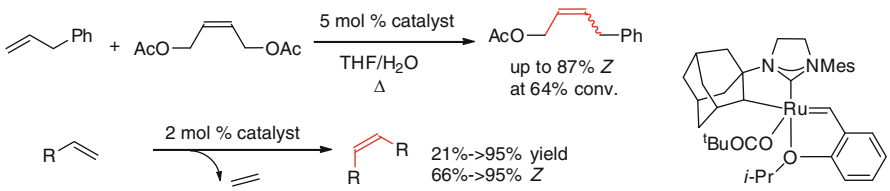

Fig. 31 New Ru-carbene catalyst for highly *Z*-selective olefin metathesis reactions

6 Miscellaneous Reactions with Generation of *Z*-Alkenes

6.1 Elimination Reactions

Elimination reactions have been traditionally used for olefin synthesis; one such example (essentially the second step of Peterson olefination) is shown in Fig. 32 [71]. Reactions of this type take advantage of the high stereoselectivity of the elimination step. However, the control of the alkene geometry in the product necessitates the diastereopurity of the starting material, access to which is arguably more difficult. This limits the application of this method to special cases. One example of Grob fragmentation to yield a trisubstituted *Z*-alkene as a key step in natural product synthesis is shown in Fig. 33 [72]. Thus, saponification induced a decarbonylation-*trans*-elimination sequence to provide the trisubstituted alkene as a single *Z*-isomer.

Su and co-workers reported an interesting Sc-catalyzed reaction of ketones with benzoyl chloride to produce aryl-*Z*-vinyl chlorides (Fig. 34) [73]. While $Sc(OTf)_3$ activated the carbonyls towards attack by the acid chloride, bis(trichloromethyl) carbonate (triphosgene) regenerated the benzoic chloride catalyst from the benzoic acid side product. All the products in this report were obtained as pure *Z*-isomer. A transition state model was proposed to account for the stereoselectivity of the system, in which *cis*-elimination took place through a six-membered chair transition state with the substituents on the substrate residing at the equatorial position.

6.2 Rearrangement Reactions

Rearrangement reactions that involve alkenes (e.g., Wittig rearrangement and Claisen rearrangement) have the potential for delivering alkenes in a stereoselective fashion. However, in most cases the *E*-alkenes are generated predominately based on conformational control in the cyclic transition states of these reactions. Only in selected examples were *Z*-alkenes produced, where high substrate dependence is observed. As one example, Yamamoto reported a Lewis acid promoted *Z*-selective Claisen rearrangement in 1990 (Fig. 35) [74]. Up to 97:3 *Z*:*E* was obtained for the alkene products using the sterically bulky Al-based Lewis acid.

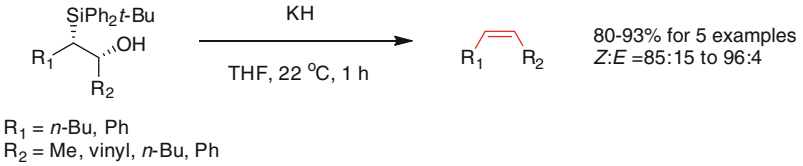

Fig. 32 Elimination of α-silyl alcohol to yield *Z*-alkenes

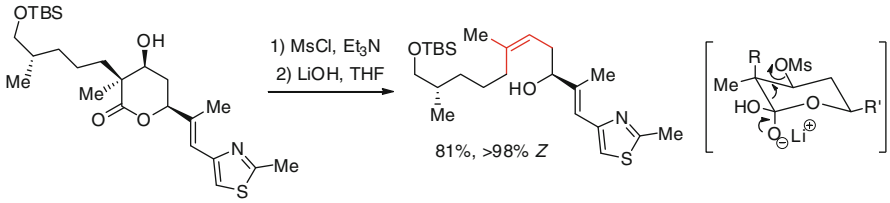

Fig. 33 Grob fragmentation to yield trisubstituted *Z*-alkene

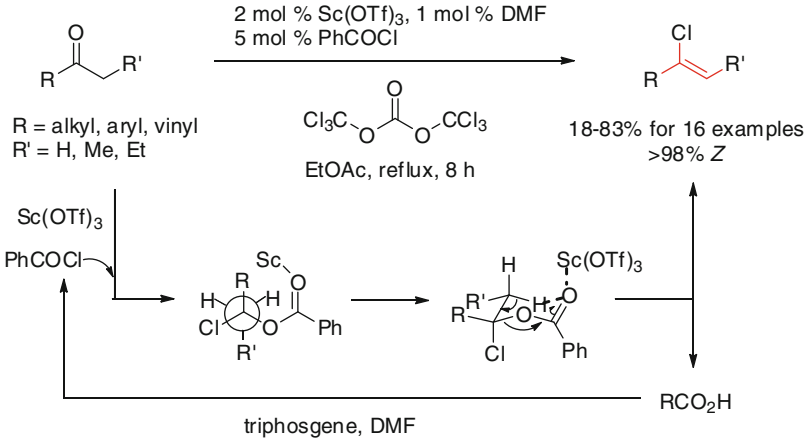

Fig. 34 Sc-catalyzed formation of alkenyl chlorides from ketones

6.3 Allylic Substitution/Allylation Reactions

Basavaiah [75] reported in 1992 that allylic reduction of allyl acetates with a α-CN substituent yielded the vinyl cyanide products in complete *Z*-selectivity (Fig. 36). One decade later, Kabalka reported that Pd-catalyzed allylic substitution of similar substrates using *p*-TolBF_3K also led to the products as an exclusive *Z*-isomer (Fig. 37) [76]. The CN group was necessary for *Z*-selectivity and the substrate scope was limited in both systems.

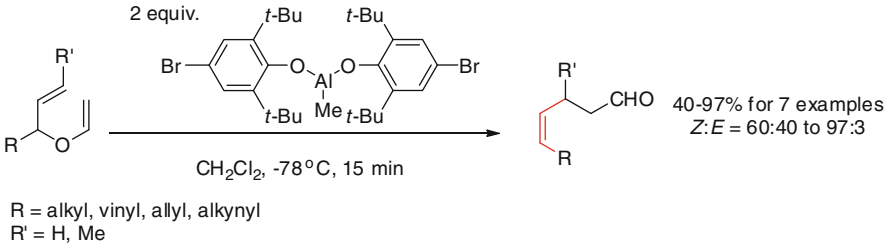

Fig. 35 Lewis acid promoted *Z*-selective Claisen rearrangement

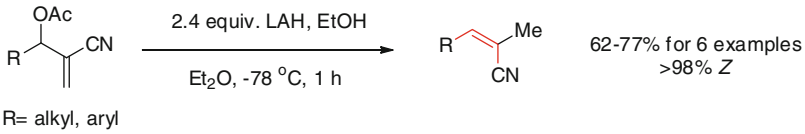

Fig. 36 *Z*-Selective allylic reduction of α-CN allyl acetates

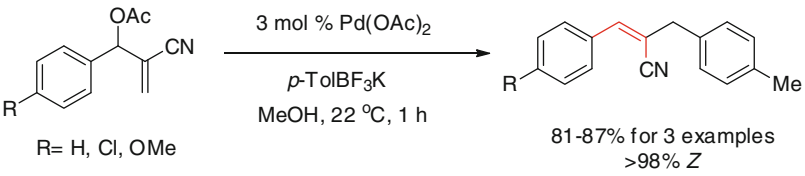

Fig. 37 *Z*-Selective allylic substitution of α-CN allyl acetates

Shibasaki and Kumagai reported the catalytic asymmetric addition of allyl cyanide to ketoimines [77] and ketones [78]. As shown in Fig. 38, different regioselectivities were obtained for these two substrate types. Alkenes in the products, however, are all produced predominantly as the *Z*-isomer. The Cu catalyst and the lithium salt work together to render this reaction feasible, with high enantioselectivities obtained for a range of substrates. The origin of the *Z*-selectivity was rationalized by the pseudo-axial orientation of CN group in the six-membered-ring transition state of allyl Cu addition to the ketones [79].

7 Conclusions

Stereoselective synthesis of *Z*-alkenes represents a significant challenge in synthetic organic chemistry. While many methods, especially catalytic systems, have been developed towards this goal, Wittig olefination/Still–Gennari modified HWE reactions and heterogeneous partial reduction of alkynes have proved to be the most widely used and reliable methods for accessing *Z*-alkenes in complex molecule synthesis. The recent development of highly *Z*-selective olefin metathesis

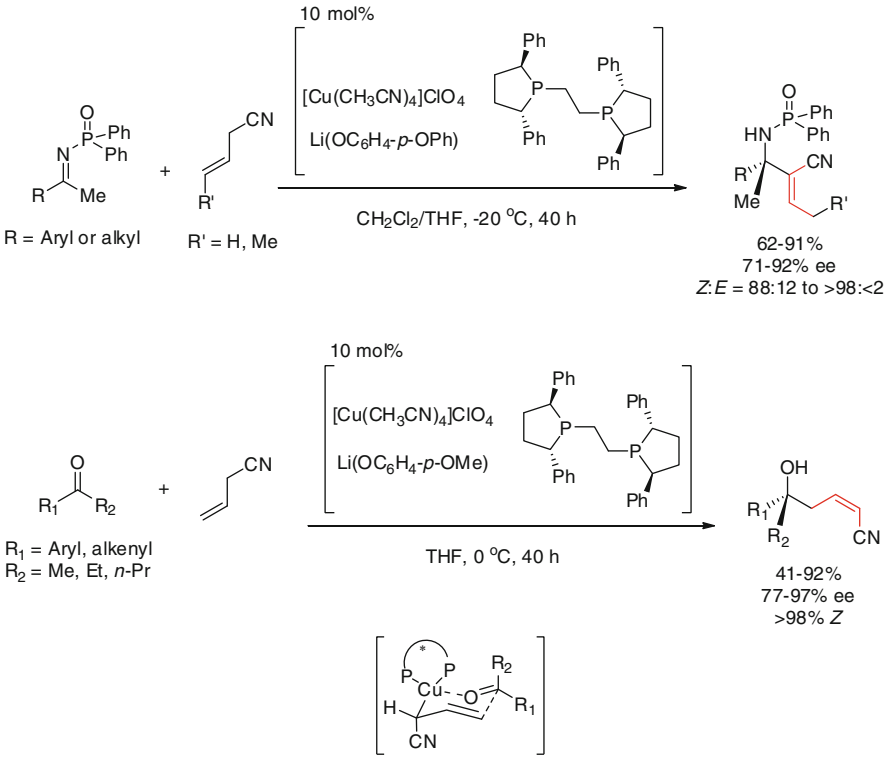

Fig. 38 Asymmetric addition of allylic cyanide to ketoimines and ketones

represents the most exciting advances in this area of research; application of this methodology to more efficient and selective preparation of complex molecules has been demonstrated through a few elegant examples. With the introduction of more robust and user-friendly catalysts, this method will certainly find more use in organic synthesis.

Acknowledgments We are grateful to National University of Singapore and National Research Foundation of Singapore for their support of our research program.

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Top Curr Chem (2012) 327: 59–86
DOI: 10.1007/128_2012_317

Published online: 20 April 2012

Stereoselective Synthesis of Mono-fluoroalkenes

Shoji Hara

Abstract Recent developments in the stereoselective synthesis of fluoroalkenes, which include hydrofluorination of alkyne, fluorination of alkenylmetal, condensation methods, dehydrofluorination of *gem*-difluoro compounds, and a cross-coupling reaction using fluorohaloalkenes or fluoroalkenylmetal, are described in this chapter.

Keywords Condensation · Cross-coupling · Elimination · Fluoroalkene · Hydrofluorination · Stereoselective synthesis

Contents

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1 Introduction

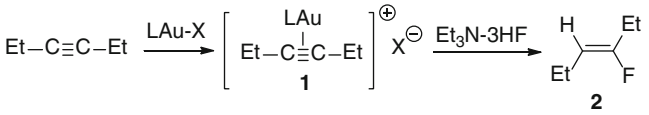
The introduction of a fluorine atom to bioactive compounds can modify their activity, so much effort has been invested in the development of selective fluorination reactions. Many bioactive compounds that have double bonds are known, and their analogs, which have a fluorine atom at their double bond, have been attracting the attention of biochemists and organic chemists [1–4]. In order to induce an effect on the activity of bioactive compounds, a fluorine atom must be introduced to the desired position at the double bond with the correct stereochemistry. The stereoselective synthesis of fluoroalkene is therefore important. There have been articles written recently that concern fluoroalkene synthesis [5–7] so I would like to introduce the recent development in the stereoselective synthesis of mono-fluorinated alkenes.

2 Hydrofluorination of Alkyne

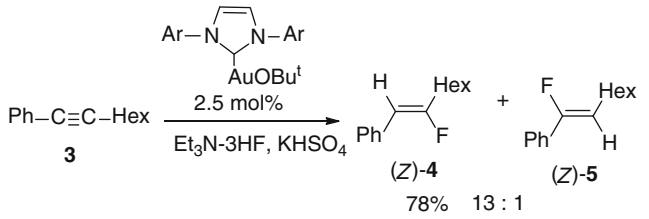
The hydrofluorination reaction of alkynes is the most direct method to synthesize fluoroalkenes. However, it is difficult to produce a fluoroalkene from a non-activated alkyne through a non-catalyzed hydrofluorination reaction. This is because strongly acidic HF reagents, such as pyridinium poly(hydrogen fluoride) (30% pyridine–70% HF), are required for the synthesis and 2 equiv. of HF adds to the triple bond to give a *gem*-difluoride under the acidic conditions [8, 9]. The non-catalyzed hydrofluorination reaction is effective only for producing fluoroalkenes having an electron-withdrawing group [10, 11].

2.1 Metal-Catalyzed Hydrofluorination Reaction

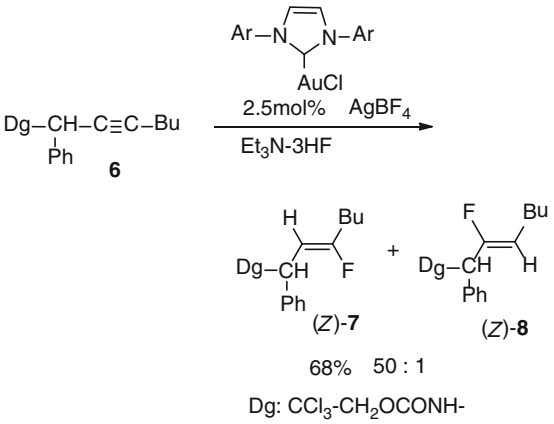
A gold complex catalyzed hydrofluorination of non-activated alkyne was reported recently [12]. Initially, the gold catalyst forms a complex **1** with an alkyne, and subsequent reaction of **1** with a fluoride yields a fluoroalkene **2**. A less acidic Et_3N-3HF was used as a fluoride source, and (*Z*)-fluoroalkene was stereoselectively formed by *trans*-addition of HF to the triple-bond (Scheme 1). With aryl alkyl acetylene **3**, the HF addition occurred regioselectively to give a (*Z*)-1-aryl-2-fluoro-1-alkene **4** as a main product (Scheme 2). The regiochemistry of the HF addition can be controlled more effectively by introducing a directing group (Dg) in the substrate [13]. A carbamate group serves as an effective directing



Scheme 1 Au catalyzed hydrofluorination of alkyne



Scheme 2 Regioselective hydrofluorination of aryl alkyl acetylene

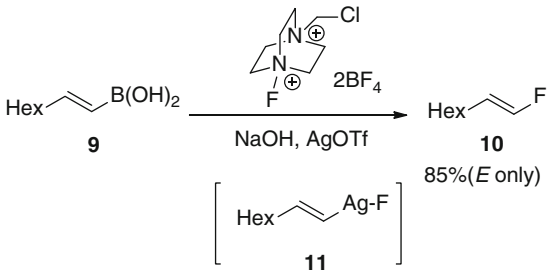


Scheme 3 Regioselective hydrofluorination of alkyne having a directing group

group; it coordinates to the Au catalyst and controls the regiochemistry of HF addition. In the reaction with an alkyne **6** which has a directing group, a fluorine atom is selectively introduced to a carbon positioned distant from the directing group (Scheme 3). The gold or palladium catalyzed fluorination of functionalized alkynes was also reported [14–16].

3 Fluorination of an Alkenylmetal with an Electrophilic Fluorination Reagent

The fluorination of alkenylmetal reagents using electrophilic fluorination reagents such as Selectfluor™ [17, 18], XeF_2 [19–21], and *N*-fluoro-*N*-alkylsulfonamide [22] has been well studied for the stereoselective synthesis of fluoroalkene.



Scheme 4 Stereoselective synthesis of fluoroalkene by fluorination of alkenylboronic acid

However, the method has serious drawbacks. During fluorination of the alkenylmetal species, an alkene is formed as a by-product and it is difficult to separate this from the fluoroalkene [19–22]. Moreover, the fluorination of alkenylmetal species such as alkenylsilane and alkenylborane proceeds non-stereoselectively, and a mixture of stereoisomers is formed [17, 18]. Recently Ritter et al. reported that the fluorination of alkenylboronic acid **9** with Selectfluor™ proceeds stereoselectively and (*E*)-1-fluoroalkene **10** can be obtained stereoselectively [23] (Scheme 4). The use of AgOTf is critical for the stereoselective synthesis of fluoroalkene and the formation of undesired alkene was not observed under these conditions. The alkenylsilver species **11** was postulated as an intermediate.

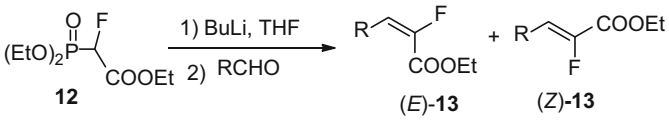
4 Condensation Reaction

The Wittig reaction of a fluoromethylidene or a fluoroalkylidenephosphonium ylide with an aldehyde afforded a fluoroalkene with poor stereoselectivity [24–28]. The Wittig reaction is therefore not helpful itself for the stereoselective synthesis of fluoroalkenes, but modifications of the Wittig reaction have been reported to achieve stereoselective synthesis of fluoroalkenes [29].

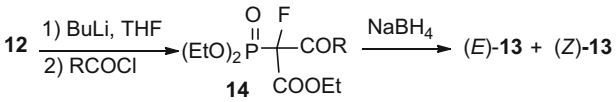
4.1 Horner–Wadsworth–Emons Reaction

Horner–Wadsworth–Emons reaction (HWE reaction) of triethyl 2-fluorophosponoacetate **12** with an aldehyde stereoselectively yields an (*E*)-α-fluoro-α,β-unsaturated ester **13** [30], and it has been used to synthesize a fluorinated analog of natural compounds [31–33]. Nagao et al. reported recently that the (*Z*)-isomer of α-fluoro-α,β-unsaturated ester **13** can be prepared stereoselectively by the reduction of triethyl 2-acyl-2-fluoro-2-phophonoacetate **14** with $NaBH_4$ at low temperature [34]. As the starting compound **14** can be prepared by the acylation of **12**, both (*E*)- and (*Z*)-**13** can be prepared from **12** stereoselectively [34] (Table 1).

Table 1 Stereoselective synthesis of (*E*)- and (*Z*)-α-fluoro-α,β- unsaturated ester **13** by HWE reaction using **12**



R	Yield of **13** (%)	*E* : *Z*
$Ph(CH_2)_2$	77	92 : 8
	81	91 : 9
^tBu	37	97 : 3
Ph	84	93 : 7



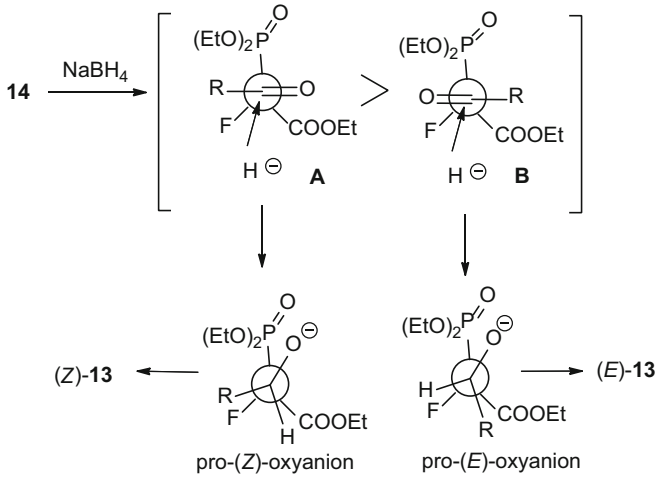
R	Yield of **14** (%)	Yield of **13** (%)	*E* : *Z*
$Ph(CH_2)_2$	60	76	<1 : >99
	77	84	9 : 91
^tBu	60	58	4 : 96
Ph	52	59	0 : 100

This selectivity was explained by the Felkin–Anh model in which the reduction of **14** proceeds through a conformation **A** to minimize the sterical interaction, and (*Z*)-**13** was formed by *syn*-elimination of oxygen and phosphine from the resulting pro-(*Z*)-oxyanion intermediate (Scheme 5). A low temperature reduction (−78 °C) is critical for obtaining (*Z*)-**13** selectivity.

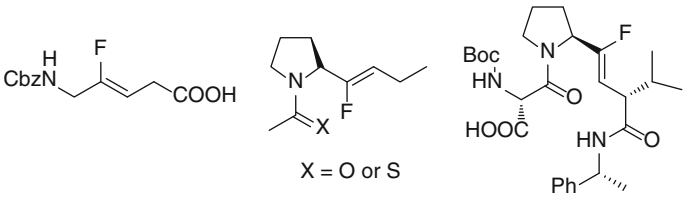
This method has been used for the synthesis of peptide isosteres having a (*Z*)-fluoroalkene moiety [34–37] (Scheme 6).

4.2 Fluoro–Julia Olefination Reaction

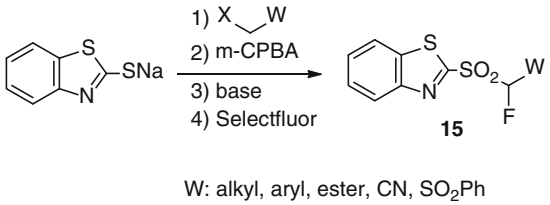
Recently, fluoro–Julia olefination reaction using α-fluorinated heteroaryl sulfone has been actively studied for the synthesis of fluoroalkene [38]. Fluorinated



Scheme 5 Reaction mechanism of (*Z*)-fluoroalkene formation by the reduction of **14**

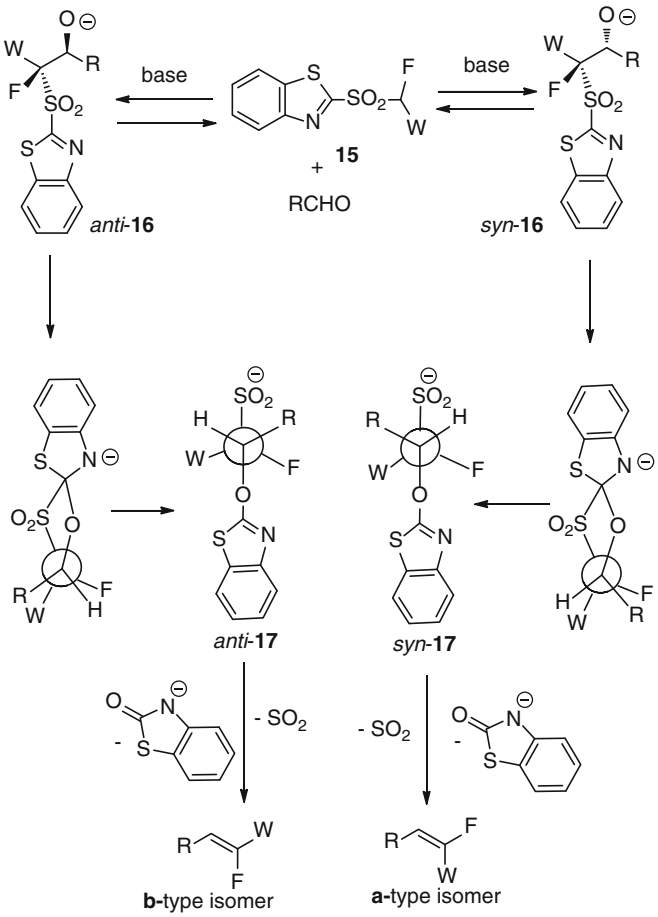


Scheme 6 Peptide isosters having a (*Z*)-fluoroalkene moiety synthesized by Nagao method



Scheme 7 Fluorinated benzothiazolyl sulfone synthesis

benzothiazolyl sulfones (BT-sulfone) **15** are most frequently used as starting materials and can be prepared from 2-methcapto-1,3-benzothiazole in three steps [39]. The method is also applicable for the synthesis of various fluorinated heteroaryl sulfones (Scheme 7).

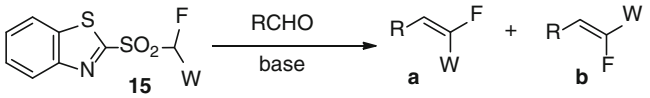


Scheme 8 Mechanism of fluoro-Julia olefination reaction

The reaction of **15** with aldehyde in the presence of a base afforded fluoroalkenes in good yield. The mechanism of the fluoro–Julia reaction is as follows. The carbanion of **15** is added to an aldehyde in either *syn* or *anti* fashion to afford *syn* or *anti* β-alkoxy sulfone **16**, respectively. The β-alkoxy sulfone **16** changes to a sulfonate **17** through a spiro-cyclic intermediate (Smiles rearrangement), and the subsequent concerted *anti*-elimination of sulfur dioxide and 2-oxobenzothiazolide produces **a**- or **b**-type fluoroalkene, respectively (Scheme 8). Generally, the stereochemistry of the product in the Julia reaction is difficult to predict, and the selectivity in the fluoro–Julia reaction is lower than that in the non-fluoro–Julia reaction [38].

In the reaction of a non-stabilized BT-sulfone anion (W = alkyl or aryl in **15**) with an aldehyde, the stereoselectivity is generally low [39, 40] (Entries 1 and 2 in Table 2). On the other hand, in the reaction of the stabilized BT-sulfone anion

Table 2 Fluoro–Julia olefination reaction using various reagents[a]

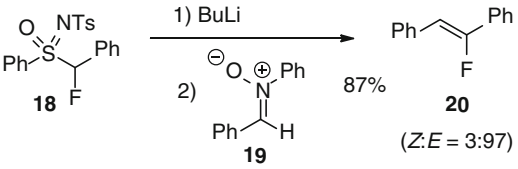


Entry	W	R	Base	Yield (%)	**a:b**
1	Me	*p*-$NO_2C_6H_4$	^{t}BuOK	88	61:39
2	Ph	2-Nap	LHMDS	100	70:30
3	COOEt	Ph	NaHMDS	53	15:85
4	COOEt	Ph	DBU	70	76:24
5	COOEt	Ph	DBU($MgBr_2$)	72	7:93
6	CN	Ph	DBU	93[b]	19:81
7	SO_2Ph	Ph	DBU	90[b]	84:16
8	COPh	*p*-$MeOC_6H_4$	DBU	61	0:100
9	CON(OMe)Me	2-Nap	DBU	84[c]	4:96
10	CON(OMe)Me	2-Nap	DBU	93	78:22
11	CON(OMe)Me	2-Nap	NaH	90	0:100

[a]If otherwise not mentioned, THF was used as a solvent
[b]CH_2Cl_2 was used as solvent
[c]DMPU was used as a solvent

(W = electron-withdrawing group in **15**) with an aldehyde, better stereoselectivity can be expected. However, the stereochemistry of the product and the selectivity are dependent on the reaction conditions and the type of electron-withdrawing group in **15**. When DBU was used as a base in the reaction of **15** (W = COOEt), an **a**-type fluoroalkene was formed as the main product [41, 42] (Entry 4). On the other hand, when NaHMDS or DBU with $MgBr_2$ was used, a **b**-type isomer was formed selectively [40] (Entries 3 and 5). The difference in selectivity was explained by the difference in their transition state. When DBU was used, the reaction proceeds through a non-chelated open-chain transition state to provide a *syn*-β-alkoxy sulfone **16**, which is a precursor of the **a**-type isomer. On the other hand, when NaHMDS or DBU with $MgBr_2$ was used, the reaction proceeds through a chelated chair-like transition state to afford an *anti*-β-alkoxy sulfone **16**, which is the precursor of the **b**-type isomer (Scheme 8). In the reaction using the phenylsulfonyl group substituted **15** (W = SO_2Ph), a similar selectivity was observed [43] (Entry 7). However, when a cyano or keto group substituted substrate was used (W = CN or COPh) with DBU, the **b**-type isomer was selectively formed [44, 45] (Entries 6 and 8). Furthermore, when *N*-methoxy-*N*-methyl amide (Weinreb amide) is used, the selectivity of the reaction and stereochemistry of the product are highly dependent on the reaction conditions [45] (Entries 9–11).

The reaction of an α-fluorosulfoximine **18** with a nitrone **19** was also reported, and (*Z*)-fluoroalkene **20** was formed in good yield with high stereoselectivity [46] (Scheme 9).



Scheme 9 Reaction of α-fluorosulfoximine with a nitrone

5 Reductive Elimination Reaction of *poly*-Halo Compounds

The reductive elimination reaction of *poly*-halo compounds has been used to make fluoroalkenes stereoselectively. Recently, the method was successfully used to prepare amino acids having a (*Z*)-fluoroalkene moiety **22**, fluoroalkene dipeptide isosteres (FADIs), which are currently attracting much attention as nonhydrolyzable peptide mimics [4, 47, 48]. The (*Z*)-fluoroalkene moiety was synthesized by the reductive defluorination reaction of γ,γ-difluoro-α,β-unsaturated ester **21** using Me_2CuLi or SmI_2. As the reaction proceeds through a fluorodienolate intermediate **23**, the introduction of a substituent at the α-position of the ester group is possible by the addition of an electrophile [49–56] (Scheme 10). When Me_3Al is used with Cu salt in a reaction with **21**, an S_N2' type reaction occurs to give (*Z*)-**22** (E = Me) directly [57–59].

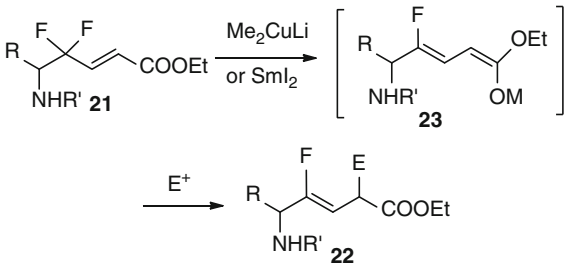
5.1 *Reductive Defluorination of Allylic* gem-*Difluorides Using Pd Catalyst*

When an allylic *gem*-difluoride **24** is treated with Pd catalyst and $PhSiH_3$ in EtOH, a reductive defluorination reaction occurs to give FADIs **25**. The reaction proceeds through a π-allyl palladium intermediate **26**. When an electron-withdrawing group is attached to the double bond, the (*Z*)-isomer is formed selectively (Entries 1–3 in Table 3). However, when an electron-withdrawing group is not attached, selectively is poor [60] (Entry 4).

When 1-phenyl-2,2-difluoro-3-buten-1-ol **27** was subjected to a reaction with a Pd catalyst in the presence of *sec*-amine, the amine attacked the π-allyl intermediate to give aminated (*Z*)-fluoroalkene **28** stereoselectively [61] (Scheme 11).

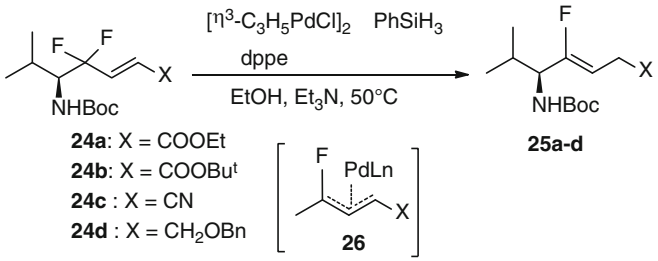
5.2 *Reductive Defluorination of Allylic* gem-*Difluorides by Intramolecular Redox Reaction*

Otaka et al. reported that the reaction of γ,γ-difluoro-α,β-enal **24e** with an *N*-heterocyclic carbene (NHC) generated from thiazolium salt **29** gave FADI **25a** in moderate yield. When enoylsilane **24f** was used in the reaction with an NHC generated from **30**, the result was improved and **25a** was obtained in good yield with high stereoselectivity (*Z*:*E* = 96:4) [62] (Table 4).

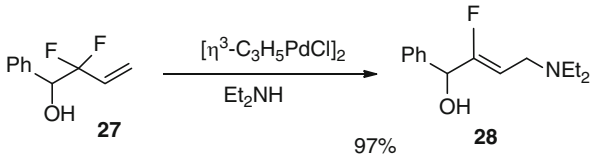


Scheme 10 Reductive defluorination of allylic *gem*-difluoride using a metallic reagent

Table 3 Reductive defluorination using Pd catalyst



Entry	**24**	Yield (%)	*Z*:*E*
1	**24a** (X = COOEt)	99	91:9
2	**24b** (X = $COOBu^t$)	91	>97:3
3	**24c** (X = CN)	73	86:14
4	**24d** (X = CH_2OBn)	77	50:50

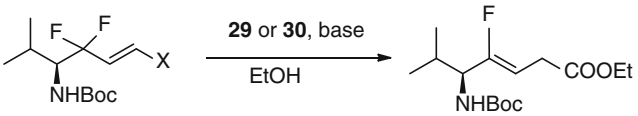


Scheme 11 Reductive defluorination of allylic *gem*-difluoride using Pd catalyst

The reaction includes the intramolecular redox mechanism. Initially, the addition of NHC to the carbonyl group occurred to give an adduct **31**, and the subsequent 1,2-shift of the proton or sily group (Brook rearrangement) from the carbon to oxygen took place to give an allylic anion species **32**. The reductive elimination of fluoride from **32** gave fluorodienoate **33**, which in turn gave **25a** by ethanolysis (Scheme 12).

The aminolysis of dienolate **33** was also performed to obtain an amide-type FADIs **34** [63]. The NHC generated from the thiazolium salt **30** or triazolium salt was not effective and a cyanide ion was found to be suitable for the aminolysis. The reaction of **24f** with KCN in the presence of 18-crown-6, and subsequent

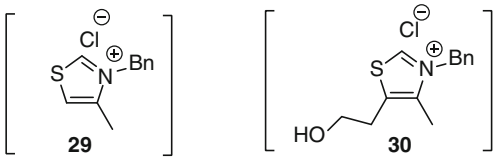
Table 4 Reductive defluorination by intramolecular redox reaction mediated by NHCs

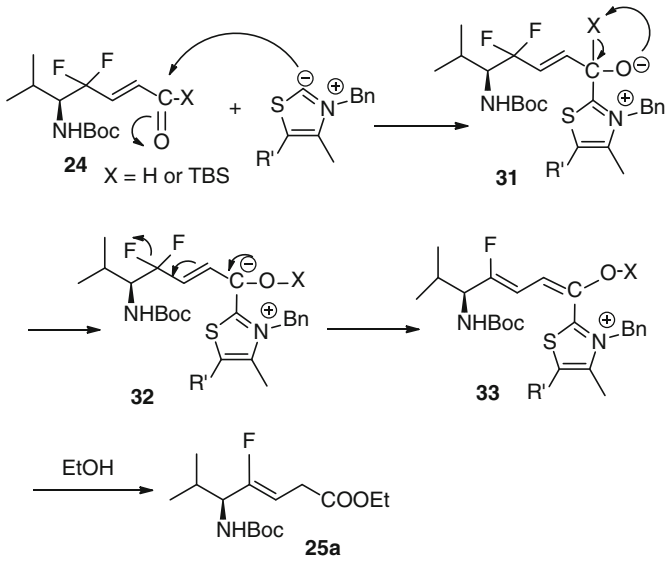


24e: X = CHO
24f: X = COTBS

25a

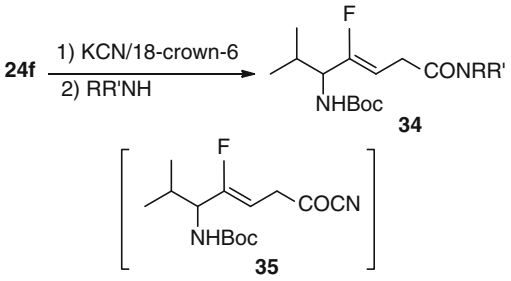
24	29 or 30	base	Yield (%)	Z : E
24e (X = CHO)	**29**	$^{i}Pr_2NEt$	66	—
24f (X = COTBS)	**30**	DBU	81	96 : 4



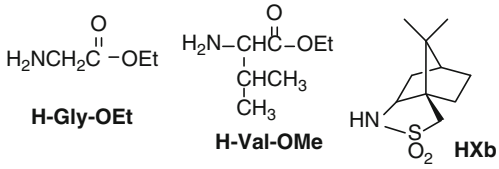


Scheme 12 Reductive defluorination of allylic *gem*-difluoride by intramolecular redox reaction

Table 5 Reductive defluorination by intramolecular redox reaction mediated by a cyanide ion



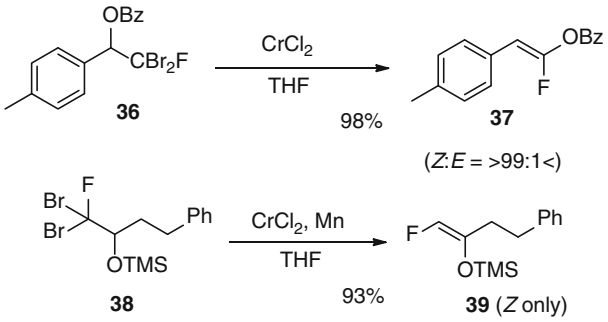
Entry	Amine	Yield (%)	*Z* : *E*
1	$BnNH_2$	85	95 : 5
2	**H-Gly-OEt**	93	94 : 6
3	**H-Val-OMe**	90	94 : 6
4	**HXb**	95	93 : 7



addition of benzylamine, gave **34** (RR'N = BnNH) in 85% yield with high (*Z*)-selectivity (*Z*:*E* = 95:5) (Entry 1 in Table 5). In this reaction, an acyl cyanide **35** must be formed as an intermediate. When an amino acid derivative such as glycine or valine (H-Gly-OEt or H-Val-OMe) is used as the amine, tripeptide isosteres can be prepared (Entries 2 and 3). The introduction of a FADI moiety to the peptide resins was also performed by using a peptide as amine.

5.3 *Reductive Dehalogenation of Dibromofluoromethyl Compounds Using $CrCl_2$*

Mioskowski et al. reported that when 2,2-dibromo-2-fluoro-1-tolylethyl benzoate **36** was treated with $CrCl_2$, (*Z*)-1-fluoro-2-(*p*-tolyl)vinyl benzoate **37** was formed stereoselectively. During the reaction, a migration of the benzoyloxy group and elimination of two bromides occurred [64]. Taguchi et al. also reported that in the reaction of a silyl ether of dibromofluoro alcohol **38** with $CrCl_2$ and Mn, a silyl enol ether of α-fluoroketone **39** having (*Z*)-stereochemistry was formed stereoselectively [65] (Scheme 13).



Scheme 13 Reductive dehaloganation of dibromofluoromethyl compounds using $CrCl_2$

6 Cross-Coupling Reaction

Transition metal catalyzed cross-coupling reactions using fluoroalkenyl halides or (fluoroalkenyl)metals are one of the most effective methods for stereoselective fluoroalkene synthesis. By choosing the appropriate fluoroalkenyl halide or (fluoroalkenyl)metal reagent, various fluoroalkenes with the desired stereochemistry and functional groups can be prepared. Therefore, much effort has been invested in the stereoselective synthesis of the starting fluoroalkenyl halides and (fluoroalkenyl)metals, as well as the cross-coupling reaction that utilizes them.

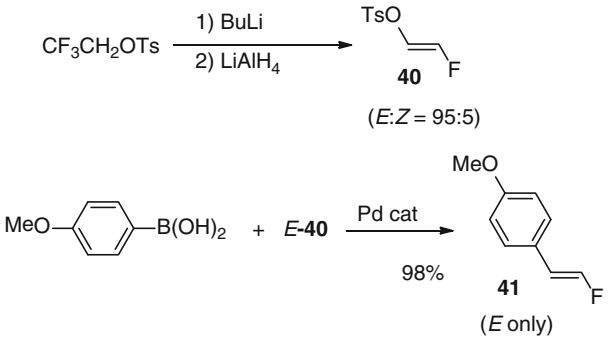
6.1 Cross-Coupling Reaction Using 2-Fluorovinyl Tosylate

(*E*)-2-Fluorovinyl tosylate **40** was stereoselectively prepared from commercially available 2,2,2-trifluoroethyl tosylate in two steps. A pure (*E*)-**40**, isolated by column chromatography, was used in the Suzuki–Miyaura coupling with (4-methoxyphenyl)boronic acid, and (*E*)-(2-fluorovinyl)-4-methoxybenzene **41** was obtained stereoselectively [66] (Scheme 14).

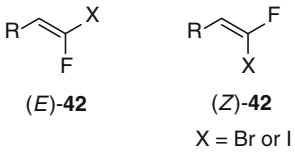
6.2 Cross-Coupling Reaction Using 1-Fluoro-1-halo-1-alkene

1-Fluoro-1-halo-1-alkene **42** is prepared by a Wittig-type reaction as a mixture of stereoisomers whose separation is rather difficult [30, 67, 68] (Scheme 15).

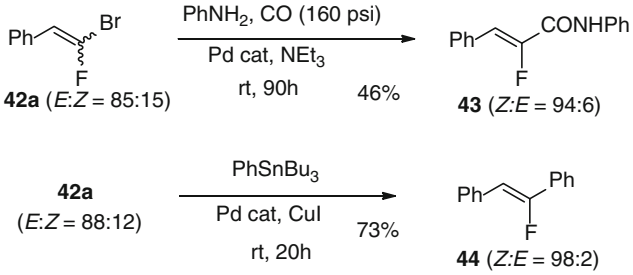
In the transition metal catalyzed cross-coupling reaction of **42**, the (*E*)-isomer reacts more quickly than the (*Z*)-isomer. Therefore, it is possible to obtain selectively the cross-coupling product derived from (*E*)-**42** by controlling the reaction



Scheme 14 Cross-coupling reaction using 2-fluorovinyl tosylate **40**



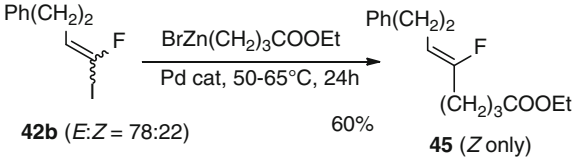
Scheme 15 (*E*)- and (*Z*)-1-fluoro-1-halo-1-alkene **42**



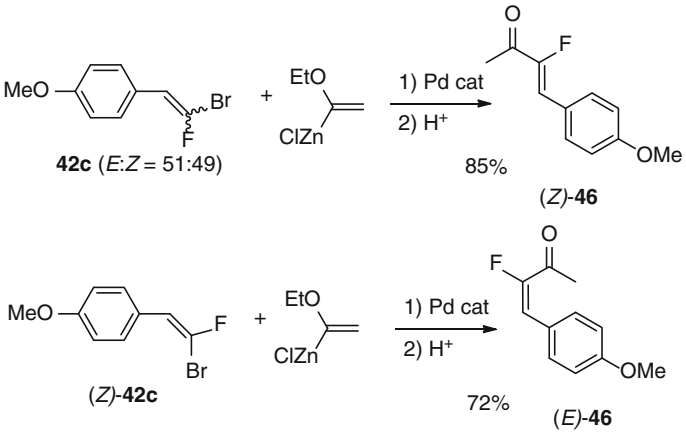
Scheme 16 Stereoselective fluoroalkene synthesis by cross-coupling reaction using 1-bromo-1-fluoro-1-alkene **42a**

conditions even when a mixture of (*Z*)- and (*E*)-**42** was used. For instance, in the carboamidation reaction of **42a** (*E*:*Z* = 85:15), (*Z*)-α-fluoro-α,β-unsaturated amide **43** was formed stereoselectively (*Z*:*E* = 94:6). It is critical to carry out the reaction at room temperature to obtain (*Z*)-**43** stereoselectively, even though a long reaction time is required [69]. Similarly, when **42a** (*Z*:*E* = 88:12) was applied to the Stille coupling with $PhSnBu_3$, the (*Z*)-isomer of fluorostilbene (**44**) was obtained stereoselectively (*Z*:*E* = 98:2) [70] (Scheme 16).

This methodology was also applied to Negishi coupling. When 1-fluoro-1-iodo-4-phenyl-1-butene **42b** (*E*:*Z* = 78:22) was subjected to the reaction with an alkyl



Scheme 17 Stereoselective fluoroalkene synthesis by Negish coupling using 1-bromo-1-fluoro-1-alkene **42b**

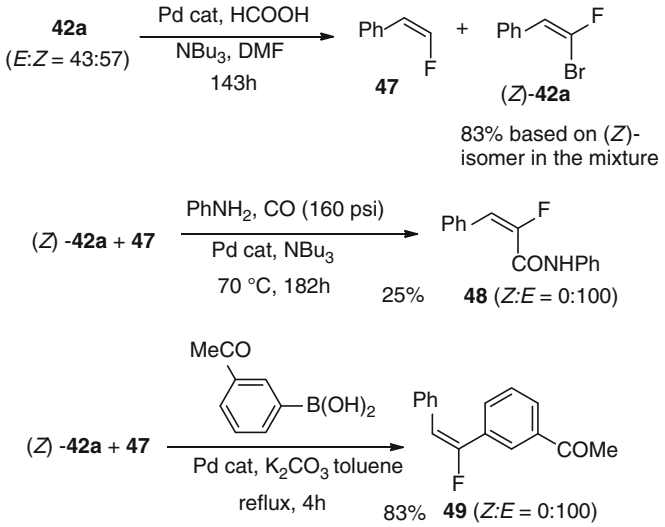


Scheme 18 Stereoselective α-fluoroenone synthesis by Negish coupling using 1-bromo-1-fluoro-1-alkene **42c**

zinc reagent in the presence of a Pd catalyst, the (*Z*)-isomer of the fluoroalkene **45** was formed exclusively [71] (Scheme 17).

Pannecoucke et al. also reported the selective synthesis of (*E*)- and (*Z*)-α-fluoroenone **46** by the Negishi coupling of 1-bromo-1-fluoro-1-alkene **42c** with an ethoxyvinylzinc reagent. When a (*Z*)-isomer of the α-fluoroenone **46** is desired, an excess amount of a mixture **42c** was used. Under these conditions, (*E*)-**42c** reacted more quickly than the (*Z*)-isomer, and (*Z*)-α-fluoroenone **46** was formed selectively, while (*Z*)-**42c** remained unchanged. Therefore, pure (*Z*)-**42c** could be obtained from the reaction mixture and was used for the synthesis of (*E*)-**46** by reaction with the ethoxyvinylzinc reagent [72] (Scheme 18).

Burton et al. reported that when a mixture of (*E*)- and (*Z*)-**42a** is reduced with $HCOOH/NBu_3/Pd(II)/DMF$, an (*E*)-isomer is reduced to 1-fluoro-1-alkene **47** more quickly than the (*Z*)-isomer, and, as the result, pure (*Z*)-**42a** can be obtained [73]. Practically, the separation of (*Z*)-**42** is not necessary for the application to the cross-coupling reactions because **47** is inert to the cross-coupling reactions under standard conditions. Therefore, when the mixture of (*Z*)-**42a** and **47** was subjected to the carboamidation reaction, the (*E*)-isomer of the α-fluoro-α,β-unsaturated amide **48** was stereoselectively formed with moderate yield [69]. Similarly, when a mixture was used for the Suzuki–Miyaura coupling with arylboronic acid, the (*E*)-isomer of fluorostilbene derivative **49** was obtained stereoselectively [70] (Scheme 19).



Scheme 19 Synthesis of (*Z*)-1-bromo-1-fluoro-1-alkene **42a** and its application to cross-coupling reactions

6.3 *Cross-Coupling Reaction Using (1-Fluoro-1-alkenyl)metal Reagents*

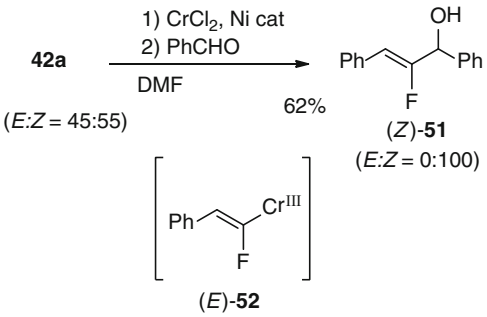
An effective method for the stereoselective synthesis of an (*E*)- or (*Z*)-(1-fluoro-1-alkenyl)metal reagent **50** has not yet been reported (Scheme 20). McCathy et al. reported the stereoselective synthesis of (1-fluoro-1-alkenyl)stannane (M = Sn in **50**) from the corresponding 1-fluoro-1-alkenyl sulfone and used it for the stereoselective synthesis of fluoroalkene by Stille coupling. However, the starting alkenyl sulfone was prepared as a mixture of stereoisomers and a pure isomer was obtained by separation using column chromatography [74–76].

In the chromium-mediated reaction of 1-fluoro-1-bromo-1-alkene with an aldehyde, the (*E*)-isomer reacts more quickly than the (*Z*)-isomer. Therefore, when a mixture of stereoisomer **42a** was subjected to the reaction with benzaldehyde in the presence of $CrCl_2$ and Ni catalyst, a (*Z*)-isomer of allylic alcohol **51** was selectively formed [77, 78] (Scheme 21). The reaction proceeds through an alkenylchromium species **52**, and the formation of the (*E*)-alkenylchromium species is much faster than that of the (*Z*)-isomer. Actually, the reaction of a pure (*Z*)-isomer of 1-fluoro-1-bromo-1-alkene with aldehyde is sluggish, and the corresponding (*E*)-isomer of the product was obtained in low yield or not obtained at all. Therefore, a good method for the synthesis of (*E*)-**51** has not yet been reported.

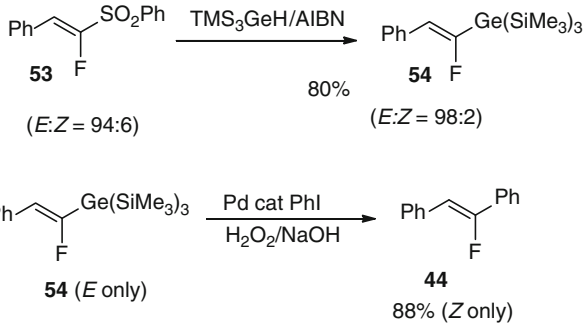
Wnuk et al. synthesized an (*E*)-(fluoroalkenyl)germane species **54** from a corresponding fluoroalkenyl sulfone **53** as in the synthesis of the (fluoroalkenyl) stannane [74–76], and the resulting (*E*)-(fluoroalkenyl)germane **54** was used in the cross-coupling reaction [79]. In the reaction of **54** with iodobenzene,

50a **50b**

Scheme 20 (*E*)- and (*Z*)-1-fluoro-1-alkenyl metal reagent **50**



Scheme 21 Reaction of **42a** with benzaldehyde in the presence of $CrCl_2$ and Ni catalyst

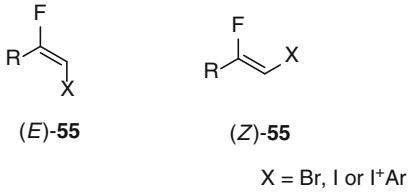


Scheme 22 Synthesis of (*E*)-(fluoroalkenyl)germane **54** and its application to cross-coupling reaction

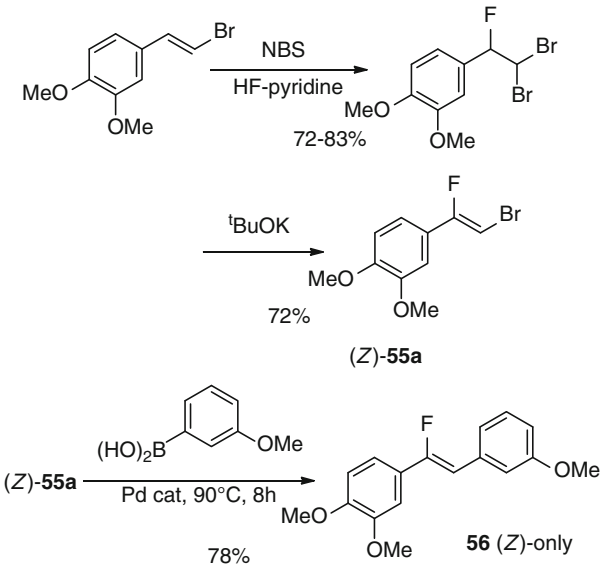
(*Z*)-fluorostilbene **44** was formed stereoselectively in good yield. However, when bromobenzene was used, the yield of **44** decreased to 24% and a homo-coupling product was formed as a main product (Scheme 22).

6.4 Cross-Coupling Reaction Using 2-Fluoro-1-halo-1-alkenes or (2-Fluoro-1-alkenyl)iodonium Salts

(*E*)-2-Fluoro-1-halo-1-alkene **55** can be prepared from 1-alkyne by the reaction with IF generated in situ (X = I) or BrF (X = Br) [80–82], and the resulting (*E*)-**55**



Scheme 23 (*E*)- and (*Z*)-2-Fluoro-1-halo-1-alkene **55**



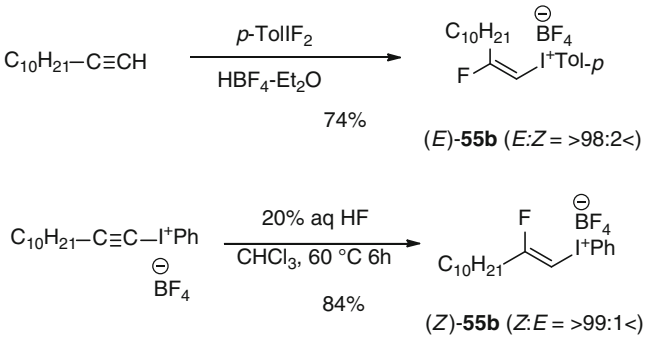
Scheme 24 Synthesis of (*Z*)-1-bromo-2-fluoro-1-alkene **55a** and its application to cross-coupling reaction

species has been used for the synthesis of various (*E*)-fluoroalkenes by applying it to the cross-coupling reaction [81, 82] (Scheme 23).

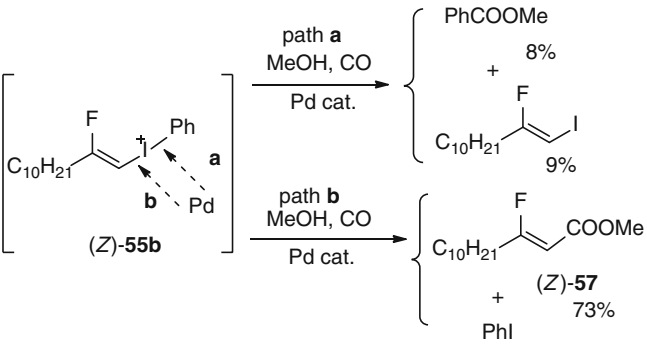
(*Z*)-2-Fluoro-1-bromo-1-alkene **55a** was prepared from 1-bromo-1-alkene by the addition of BrF, followed by treatment with a base. This method is applicable only when R is an aryl group. The resulting (*Z*)-**55a** was used in the Suzuki–Miyaura coupling for the synthesis of the (*Z*)-fluorostilbene derivative **56** [83] (Scheme 24).

Both (*E*)- and (*Z*)-(2-fluoro-1-alkenyl)iodonium salt **55** (X = I^+Ar) can be prepared stereoselectively. (*E*)-(2-Fluoro-1-dodecyl)iodonium salt **55b** is prepared by the addition of iodoarene difluoride to 1-dodecyne [84, 85]. On the other hand, (*Z*)-**55b** was prepared from the 1-dodecynyliodonium salt by a reaction with aqueous HF [86] or metal fluoride [87, 88] (Scheme 25).

In the transition metal catalyzed cross-coupling reaction, the (2-fluoroalkenyl) iodonium salt has two reactive sites, a phenyl group and a fluoroalkenyl group.



Scheme 25 Stereoselective synthesis of (*E*)- and (*Z*)-(2-fluoro-1-alkenyl)iodonium salt **55b**

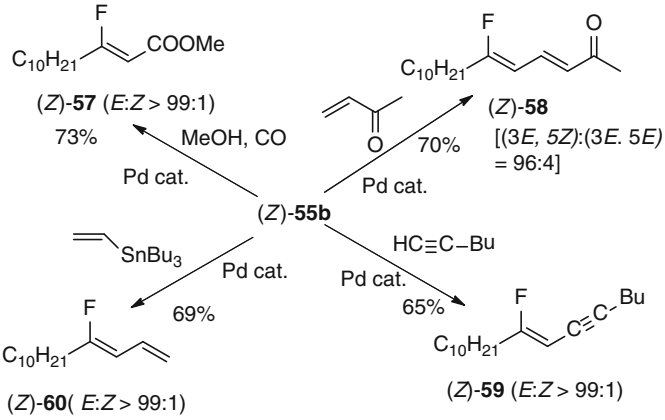


Scheme 26 Two possible reaction paths in cross-coupling reaction using **55b**

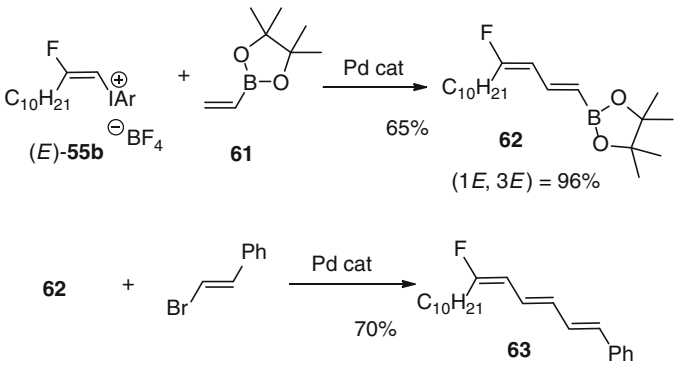
When (*Z*)-**55b** was applied to the methoxycarbonylation reaction, the (*Z*)-β-fluoro-α,β-unsaturated ester **57** was formed as a main product (73%) and methyl benzoate was formed as a minor product (8%). As the reactivity of the iodonium salt with a transition metal catalyst is higher than that of the corresponding iodide, the methoxycarbonylation reaction of neither iodobenzene nor fluoroiodoalkene occurs under these conditions. Therefore, this result shows that the oxidative addition of the catalyst to (*Z*)-**55b** selectively occurred at an alkenyl carbon–iodine bond (path **b**) [89] (Scheme 26).

Both (*E*)- and (*Z*)-**55b** can be used for cross-coupling reactions such as methoxycarbonylation, the Heck reaction, Sonogashira coupling, and Stille coupling, and the corresponding β-fluoro-α,β-unsaturated ester **57**, δ-fluoro-α,β,γ,δ-unsaturated ketone **58**, 2-fluoro-1-alkynylalkene **59**, and 4-fluoro-1,3-alkadiene **60** were successfully obtained stereoselectively [89] (Scheme 27).

The application of (*E*)-**55b** to the Heck reaction with vinylboronate **61** gave (1*E*,3*E*)-(4-fluoro-1,3-dienyl)boronate **62** stereoselectively ((1*E*,3*E*) = 96%). The resulting (fluorodienyl)boronate **62** was used in the Suzuki–Miyaura coupling and fluorotriene **63** was obtained stereoselectively [90] (Scheme 28).

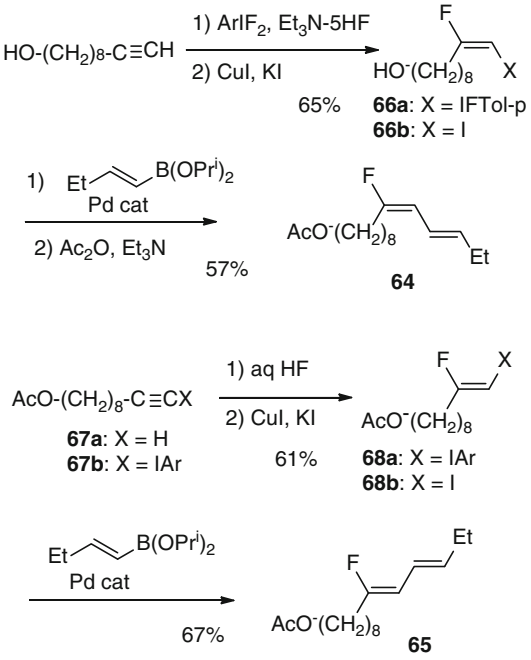


Scheme 27 Stereoselective synthesis of various fluoroalkenes by cross-coupling reactions using **55b**

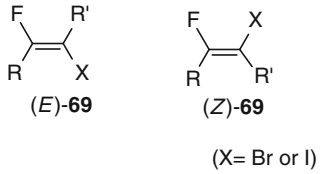


Scheme 28 Synthesis of (fluorodienyl)boronate **62** and its application to cross-coupling reaction

The Suzuki–Miyaura coupling using (2-fluoroalkenyl)iodonium salt **55** (X = I^+Ar) proceeds non-selectively and the expected fluoroalkene was formed only as a minor product [91]. Therefore, the conversion of the iodonium salt to the corresponding 2-fluoro-1-iodo-1-alkene is required for the application to the Suzuki–Miyaura coupling [85]. Thus, (9*E*,11*E*)-9-fluoro-9,11-tetradecadien-1-yl acetate **64**, a fluorinated analog of an insect pheromone, was synthesized stereoselectively by the Suzuki–Miyaura coupling of 1-butenylboronate with (*E*)-9-fluoro-10-iodo-9-decen-1-ol **66b**, prepared from the (*E*)-10-hydroxy-2-fluoro-1-decenyliodonium salt **66a**, followed by acetylation of the hydroxyl group. Similarly, its stereoisomer (9*Z*,11*E*)-9-fluoro-9,11-tetradecadien-1-yl acetate **65** was prepared by the reaction of 1-butenylboronate with (*Z*)-9-fluoro-10-iodo-9-decen-1-yl acetate **68b**, which is prepared from the corresponding iodonium salt **68a** [92] (Scheme 29).



Scheme 29 Stereoselective synthesis of fluorinated analogs of an insect pheromone



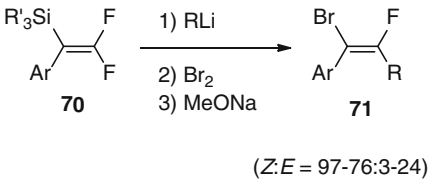
Scheme 30 (*E*)- and (*Z*)-1-fluoro-2-halo-1,2-dialkylethene **69**

6.5 *Cross-Coupling Reaction Using 1-Fluoro-2-halo-1,2-dialkylethenes*

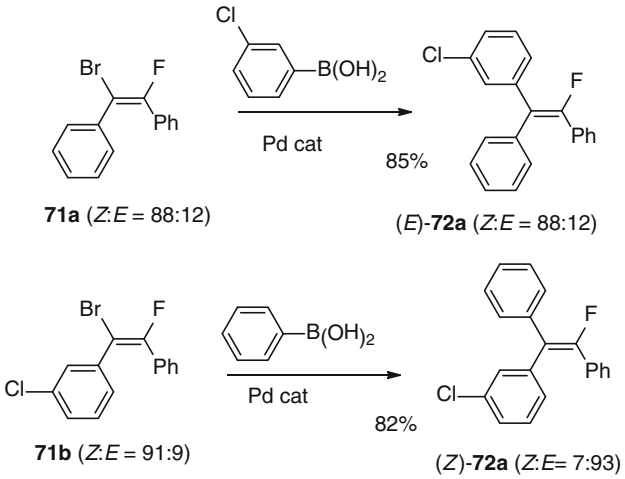
For the stereoselective synthesis of trisubstituted fluoroalkene by cross-coupling reaction, (*E*)- or (*Z*)-1-fluoro-2-halo-1,2-dialkylethene **69** is required (Scheme 30).

Paquin et al. reported the synthesis of 1-aryl-2-alkyl-1-bromo-2-fluoroethenes **71** from β,β-difluoro-α-silylstyrene derivatives **70** by alkylation, followed by bromination. With moderate to good selectivity, (*Z*)-**71** was formed (Scheme 31). The selectivity is dependent on the alkyl groups in RLi and R'$_3$Si.

The resulting (*Z*)-**71a** and (*Z*)-**71b** were used for the stereoselective synthesis of trisubstituted fluoroalkene by the Suzuki–Miyaura coupling [93] (Scheme 32).



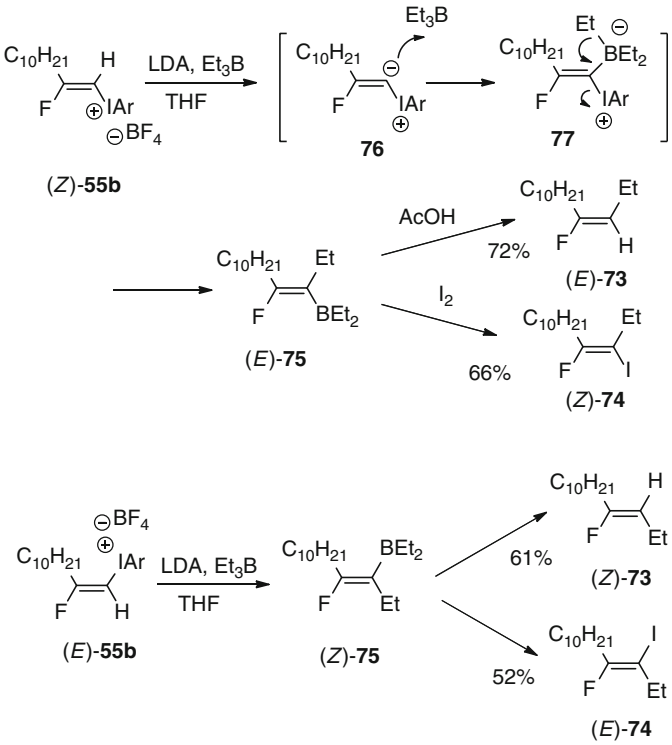
Scheme 31 Synthesis of 1-aryl-2-alkyl-1-bromo-2-fluoroethene **71**



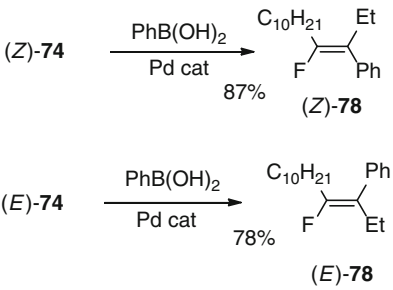
Scheme 32 Stereoselective synthesis of trisubstituted fluoroalkenes **72a** using **71**

However, in their method, the *trans*- position of the fluorine atom in **72** is always an aryl group, because the styrene derivative **70** is used as a starting material, and, furthermore, (*E*)-**71** is not accessible.

Both (*E*)- and (*Z*)-1-fluoro-2-iodo-1,2-dialkylethene **69** (X = I) can be prepared stereoselectively from (1-fluoro-1-alkenyl)iodonium salts. A vinylic proton of the (1-fluoroalkenyl)iodonium salt is acidic enough to be abstracted by a relatively weak base, because the resulting alkenyl anion species is stabilized by the formation of an iodonium ylide species [94, 95]. However, the elimination of iodoarene from the ylide species occurs to provide the alkenyl carbene species which cyclizes to fluorocyclopentene by the intramolecular C–H insertion reaction [96, 97]. When the (*Z*)-(2-fluoroalkenyl)iodonium salt **55b** was treated with LDA at low temperature in the presence of Et_3B, the generated ylide species **76** reacted with Et_3B before decomposition to the carbene, and a borate **77** was formed. Migration of an ethyl group from the borane to an adjacent carbon occurred in **77** to give (*E*)-(2-fluoroalkenyl)borane **75** stereoselectively. Protonation of (*E*)-**75** with acetic acid gave (*E*)-fluoroalkene **73**. On the other hand, when iodine was added to (*E*)-**75**, (*Z*)-fluoroiodoalkene **74** was formed stereoselectively. Similarly, (Z)-(fluoroalkenyl)



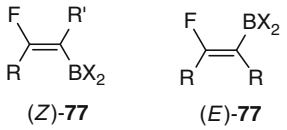
Scheme 33 Stereoselective synthesis of (*E*)- and (*Z*)-1-fluoro-2-iodo-1,2-dialkylethene **74**



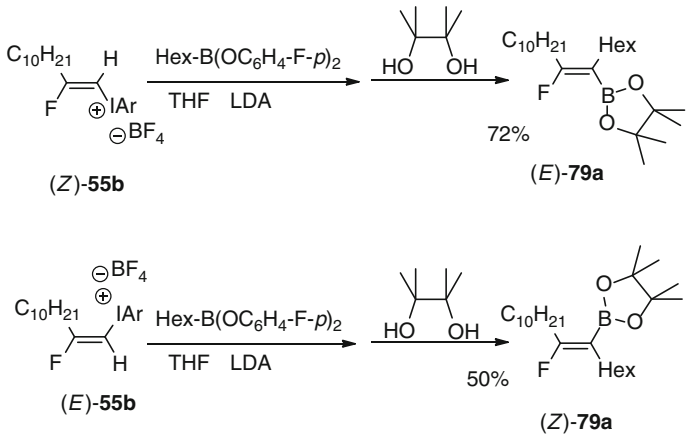
Scheme 34 Stereoselective synthesis of trisubstituted fluoroalkenes **78** using **74**

borane **75** was prepared from (*E*)-**55b**, and (*Z*)-fluoroalkene **73** and (*E*)-fluoroiodoalkene **74** were obtained stereoselectively from (*Z*)-**75** [98] (Scheme 33).

By applying (*Z*)- and (*E*)-**74** to the Suzuki–Miyaura coupling, trisubstituted fluoroalkenes (*Z*)-**78** and (*E*)-**78** were formed stereoselectively [99] (Scheme 34).



Scheme 35 (*E*)- and (*Z*)-(1,2-dialky-2-fluoroethenyl)boronate **77**



Scheme 36 Stereoselective synthesis of (*E*)- and (*Z*)-(1,2-dialky-2-fluoroethenyl)lboronate **79**

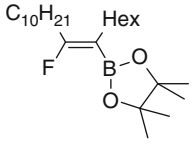
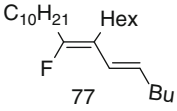
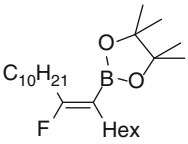
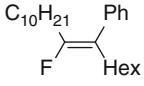
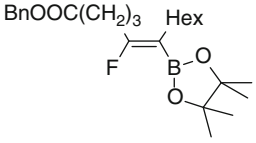
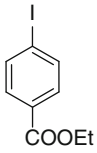
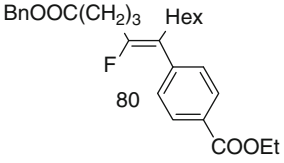
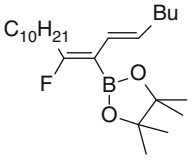
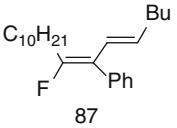
6.6 *Cross-Coupling Reaction Using (2-Fluoro-1,2-dialkylethenyl) boronates*

(*Z*)- and (*E*)-Dialkyl(fluoroalkenyl)borane **75** can be prepared from the (*E*)- and (*Z*)-(2-fluoroalkenyl)iodonium salts **55b** as shown in Scheme 33. However, the resulting **75** is not stable enough to isolate by column chromatography or recrystallization. The (fluoroalkenyl)boronate (X = OR in **77**) is more stable and suitable for isolation (Scheme 35).

When bis(*p*-phenoxy)hexylborane was used in the reaction with (*Z*)-**55b**, (*E*)-(fluoroalkenyl)boronate **79a** was obtained after transesterification to pinacol ester. The pinacol ester **79a** is stable enough to be isolated by silica gel column chromatography. Similarly, (*Z*)-**79a** can be stereoselectively prepared from (*E*)-**55b** [99] (Scheme 36).

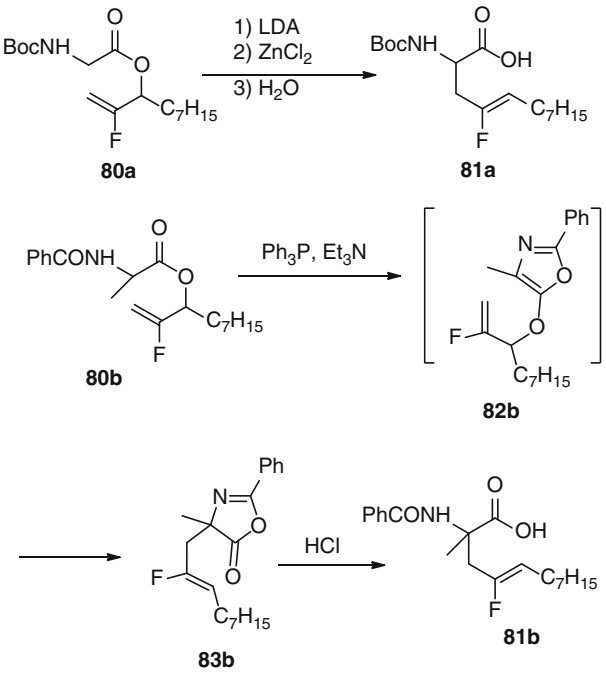
The introduction of various functional groups to **79** is possible and the resulting **79** can be used for the stereoselective synthesis of trisubstituted fluoroalkene by the application to the Suzuki–Miyaura coupling (Table 6).

Table 6 Stereoselective synthesis of trisubstituted fluoroalkenes by Suzuki–Miyaura coupling reaction using (fluoroalkenyl)boronates **79**

Boronate	Halide	Product Yield(%)
		 77
	PhI	 72
		 80
	PhI	 87

7 Fluoroalkene Synthesis Using [3.3] Sigmatropic Rearrangement

Haufe et al. used a Claisen rearrangement to prepare an amino acid having a (*Z*)-fluoroalkenyl moiety **81**. When a 2-fluoroallyl ester of *N*-Boc protected amino acid **80a** was converted to an enolate for the subsequent [3.3] sigmatropic rearrangement, the desired product **81a** was obtained in moderate yield [100]. On the other hand, when the *N*-benzolyated substrate **80b** was converted to an oxazole derivative **82b**, [3.3] sigmatropic rearrangement occurred spontaneously to give the oxazolone derivative **83b** in quantitative yield. The subsequent hydrolysis gave the desired amino acid having a (*Z*)-fluoroalkenyl group **81b** in good yield (Scheme 37) [101, 102].



Scheme 37 Stereoselective synthesis of fluoroalkene using [3,3] sigmatropic rearrangement

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Top Curr Chem (2012) 327: 87–146
DOI: 10.1007/128_2012_320

Published online: 17 April 2012

Recent Advances in Stereoselective Synthesis of 1,3-Dienes

Michael De Paolis, Isabelle Chataigner, and Jacques Maddaluno

Abstract The aim of this review is to present the latest developments in the stereoselective synthesis of conjugated dienes, covering the period 2005–2010. Since the use of this class of compounds is linked to the nature of their appendages (aryls, alkyls, electron-withdrawing, and heterosubstituted groups), the review has been categorized accordingly and illustrates the most representative strategies and mechanisms to access these targets.

Keywords Conjugated dienes · Ene–ene coupling · Ene–yne coupling · Isomerization · Organocatalysis · Stereoselective synthesis · Transition metals · Yne–yne coupling

Contents

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Abbreviations

Acac	Acetylacetone
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BOM	Benzyloxymethyl
COD	1,5-Cyclooctadiene
COT	1,3,5,7-Cyclooctatetraene
Cp	Cyclopentadiene
dba	Dibenzylideneacetone
DMB	3,4-Dimethoxybenzyl
dmfm	Dimethylfumarate
EE	Ethoxyethyl
HMDS	Hexamethyldisilazane
IPr	*N*,*N*′-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
LDA	Lithium diisopropylamide
MIP	Methoxyisopropyl
MOM	Methoxymethyl
MVK	Methylvinylketone
pin	Pinacol
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
THP	Tetrahydropyranyl
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl

1 Introduction

Conjugated dienes are the object of continuous attention in organic chemistry. These compounds are encountered in numerous natural products and find applications in many fundamental methodologies in synthesis (cycloaddition, metathesis, ene-reaction, oxidoreduction, or reductive aldolization for instance) (Fig. 1). In addition,

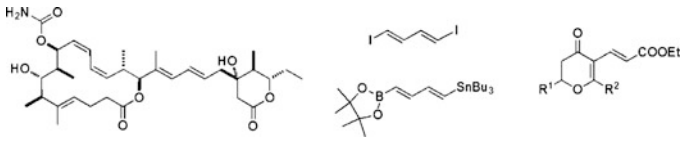


Fig. 1 Selected examples of conjugated dienes

they are employed as building blocks in polymerization processes and thus drive important developments in materials science.

Conjugated dienes are much more than just two olefins, and their reactivity is very different from that of non-conjugated dienes. The roots of this difference lie at the molecular orbitals level: compared to isolated olefins, conjugated dienes having the same substitution possess higher HOMO and lower LUMO energies which positively influence the outcome of reactions such as hydrosilylation, hydroamination, or [3+2] annulation. Since the configuration of the double bonds often influences the stereochemical course of the reactions in which 1,3-dienes are employed, stereoselective access to these precious building blocks is always welcomed.

The routes to dienes rely on multiple strategies that imply coupling methods as well as olefination. It is therefore almost impossible to depict the work done in the area through a limited number of major concepts. The methodologies employed for the synthesis of dienes, even bearing a specific class of substituents, are surprisingly diverse. This means that the sections in this chapter all follow different outlines. The general challenges to be met in the domain in the first decade of the twenty-first century remain centered on the selectivities: the configuration of each double bond of course, but also regioselectivity of the processes, particularly critical when different double bonds are involved in the reaction. In general, access to the *Z*-isomers, particularly when bulky substituents are involved, remains a problem to be solved. Transition metal-based methods have been shown to be particularly helpful in the matter.

To the best of our knowledge, there are no recent reviews dedicated to the synthesis of dienes. Papers presenting aspects of their reactivity or applications in areas of organic synthesis have appeared but none seems to be focused on the stereoselective access to these species. We have therefore chosen to build this review around the structure of the diene, and have organized the presentation according to the substituent borne by the double bonds. The objective of this chapter is to give the non-specialist reader a comprehensive overview of the most significant developments published, for major families of substituents, mostly after 2005. Four general classes of 1,3-dienes have been retained:

– Alkyl/aryl substituted dienes (including macrocyclic dienes)
– Dienes substituted by an electron-withdrawing group
– Hetero-substituted dienes (excluding halo-dienes)
– Halo-substituted dienes

We have thus organized the following in four sections. Because of obvious space limitations, the examples presented in each section correspond to the selection

made by the authors in an attempt to provide representative cases of interesting methodologies or family of compounds. This presentation is therefore not exhaustive, even for the period considered (2005–2010).

2 Stereoselective Preparation of Aryl- and/or Alkyl-Substituted Conjugated Dienes

2.1 Transition Metal-Based Methods

The metal-based preparations of conjugated dienes represent the majority of the strategies employed to attain stereoselectively 1,3-dienes connected to aryl and/or alkyl appendages. The starting material can be stereodefined when double bonds or enynes are engaged. When alkynes or allenols are employed, two double bonds are generated in a stereoselective manner.

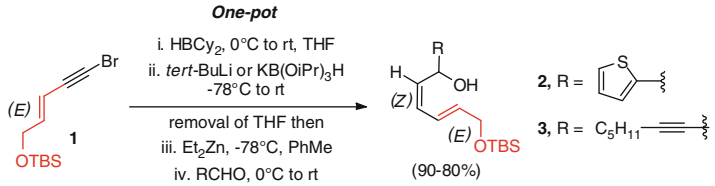
2.1.1 From Stereodefined 1,3-Enynes

The preparation of conjugated dienes from stereodefined 1,3-enynes can be carried out differently when they are bromo- or alkyl-substituted. The control of the stereoselectivity will be discussed in both cases.

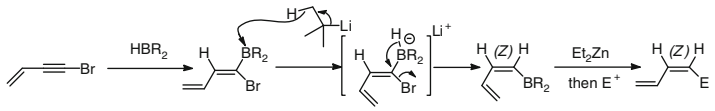
The Coupling of Bromo-Substituted 1,3-Enynes to Electrophiles

The one-pot preparation of (*Z*,*E*)-2,5-dienol was described by Walsh in 2006 [1]. The strategy is based on the sequential functionalization of bromo-substituted 1,3-enynes such as 4-bromo-1,3-enyne **1** by hydroboration followed by hydride addition to the resulting borane (steps i and ii in Scheme 1). Next, dialkylzinc and carboxaldehyde (steps iii and iv) were sequentially introduced to complete the formal addition of (*Z*)-dienyl group to an electrophile. The two aldol products **2** and **3** are illustrative of the potential of this methodology. These products contain both (*Z*)-olefin and thiophen or triple bond appendages and could, with difficulty, be prepared by conventional Lindlar reduction due to risks of catalyst poisoning by the thiophen moiety or over reduction of the triple bond.

The proposed mechanism involves the regioselective *cis*-hydroboration of the 4-bromo-1,3-enyne as observed by Zweifel [2] followed by addition of hydride, originating from *t*-BuLi [3], to initiate a 1,2-metalate rearrangement forging the C–C bond with inversion at the vinylic center (Scheme 2). This key step enables the stereospecific character of the whole process. To circumvent the low reactivity of (*Z*)-vinylborane toward aldehydes, the corresponding (*Z*)-vinylzinc was prepared by transmetalation with diethylzinc and reacted successfully with carboxaldehyde. The isolation of allylic alcohols in high yields was subordinated to a careful selection of the



Scheme 1 One-pot transformation of 4-bromo-1,3-enyne to (*Z*)-2,5-dienol



Scheme 2 Proposed mechanism for the transformation of 4-bromobut-1-en-3-yne to (*Z*)-dienes

solvents employed during the process. Thus, the hydroboration performed smoothly in polar solvent such as THF, whereas the transmetalation/electrophilic trapping needed a less polar and non-coordinating solvent such as toluene for optimal results.

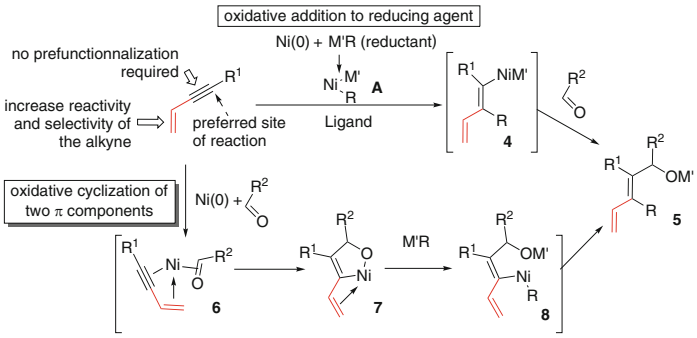
Metal-Catalyzed Coupling of 1,3-Enynes

The metal catalyzed reductive coupling of 1,3-enynes to various electrophiles is an efficient tool for the preparation of conjugated dienes connected to various functional groups (i.e., alcohols, amines). Besides their preparative steps, 1,3-enynes can be coupled to electrophiles directly and regioselectively without further functionalization steps. This constitutes an interesting improvement over the methods exploiting reactive coupling partners (i.e., organotin or organoboron), which require steps such as metalations of the precursors for their preparation. Among the existing methodologies, a brief overview of Ni- and Rh-catalyzed coupling will be presented. The putative mechanisms, scopes, and limitations will be discussed. Additionally, Au-catalyzed intramolecular coupling of 1,3-enyne and alkene will be mentioned.

Ni-Catalysis

In Scheme 3, two general mechanistic pathways that may be operative for the Ni-catalyzed coupling of 1,3-enynes with carboxaldehydes are depicted. The first pathway involves a prior oxidative addition of Ni(0) to the reductant M'R leading to a metal hydride or a metal alkyl species **A**. The reactive catalyst **A** may proceed by sequential insertion into the alkyne bond and the carbonyl bond of the electrophile to the formation of the polysubstituted 2,4-dienol **5** via vinyl nickel **4**.

The second path is initiated by an oxidative cyclization of Ni(0) with two π-components (i.e., vinylalkyne and carboxaldehyde) to form a metallacycle **7**. The transient interaction between the conjugated alkene and the transition metal in **6** may direct the regioselectivity of the metallacycle formation. A transmetalation



Scheme 3 General putative mechanisms for the Ni-catalyzed reductive coupling of 1,3-enynes to aldehydes

process would afford **8**, followed by a reductive elimination step to lead to 2,4-dienol **5**. The descriptions of these putative mechanisms are simplified and variations are possible depending on the nature of the ligands and the reducing agents employed during the process [4].

In the following cases, experimental observations are hinting at the oxidative cyclization as the preferred pathway but the nature of the ligand and the reducing agent may have an impact on the mechanistic route. Note that the stereocontrol of the process is ensured by the Ni-promoted oxidative cyclization of the π components.

The methodology implements interesting established features. First, the vinyl group (R^1) increases the reactivity of the alkyne. Second, the directing ability of the vinyl allows the preparation of substituted 1,3-dienes with very high regioselectivity. The poor regioselectivity occurring in the same conditions with alkyl-substituted alkynes is not observed.

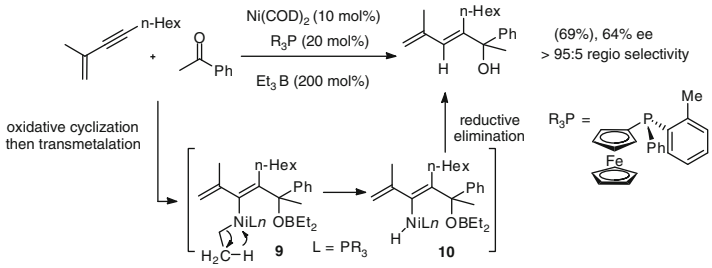
In all the cases presented in the following section, it is noteworthy that 1,3-dienes products are unreactive in the conditions of the reactions.

Montgomery and Jamison reported independently the Ni(0) catalyzed coupling of 1,3-enynes to aldehydes delivering racemic 2,4-dienol or enantiopure 3,5-dienol products from chiral epoxides [5–8].

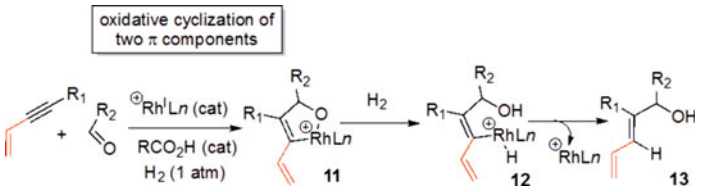
Later studies by Jamison extended this protocol to the reductive coupling of 1,3-enynes to ketones, which proceeded efficiently and with high regioselectivity. The asymmetric version of the coupling was conducted in the presence of catalytic amounts of a *P*-chiral monophosphate ligand attaining modest enantioselectivity (Scheme 4) [9]. Probably formed according to the oxidative cyclization path and transmetallated with triethylborane, the supposed intermediate **9** may have undergone, in the presence of phosphine additive, sequential β-hydride elimination/reductive elimination transformations to introduce a hydrogen-atom into the final product via **10**.

Rh-Catalysis

The cationic Rh-based catalyst systems have attracted attention to the hydrogen-mediated C–C bond formation. The preparation of functionalized 2,4-dienes from



Scheme 4 Chiral reductive coupling of 1,3-enyne to acetophenone Ni(0)-catalyzed



Scheme 5 General mechanism for the Rh-catalyzed reductive coupling of 1,3-enynes to aldehydes

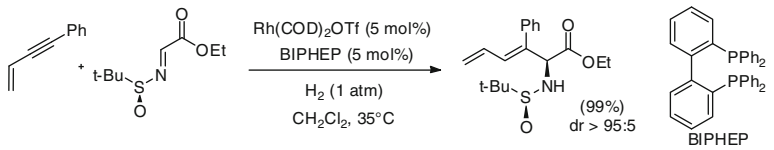
1,3-enynes by hydrogenative coupling with electrophiles has been extensively investigated by Krische [10, 11].

As for the Ni-catalyzed reductive coupling, the experimental observations of the Rh-catalyzed reductive coupling are consistent with a general mechanism shown in Scheme 5 involving oxidative cyclization of two π-components (i.e., enyne and carboxaldehyde). As a specific feature of this methodology, elemental hydrogen is employed to reduce the cationic oxarhodacyclopentene **11** into **12**. In some cases, the presence of a Brønsted acid as co-catalyst is required to enhance rate and conversion of the transformation probably by favoring this reduction step. The use of cationic rhodium or iridium catalysts is mandatory to avoid the conventional hydrogenation of the substrate. The possible explanation may lie in the lower reactivity of cationic Rh-catalyst toward elemental hydrogen, thus allowing the oxidative cyclization to take place despite the reductive environment. Reductive elimination of **12** affords 2,4-dienol **13** and regenerates the cationic Rh-catalyst.

Note that the configuration of the double bond of the 1,3-dienes prepared by this methodology is controlled by the oxarhodacyclopentene **11**.

In 2005, Krische disclosed the rhodium-catalyzed coupling of 1,3-enynes to *N*-sulfinyliminoacetate in order to reach unnatural 1,3-dienes-containing α-amino acids in a regio- and diastereoselective manner (Scheme 6) [12].

The reaction proceeded successfully with various 1,3-enynes featuring aliphatic or aromatic substitutions (Fig. 2). In all cases examined, >95:5 regio- and diastereoselectivity was achieved while no over-reduction of the products was observed.



Scheme 6 Reductive coupling of 1,3-enyne to ethyl (*N*-sulfinyl)iminoacetates

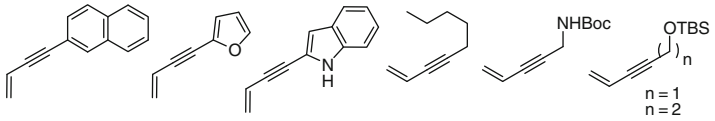
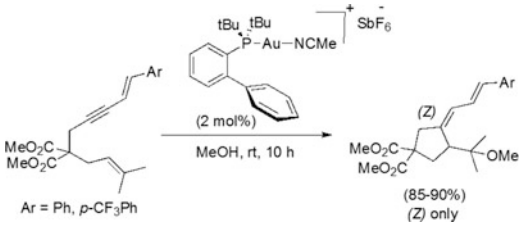


Fig. 2 1,3-Enynes examined for the rhodium-catalyzed reductive coupling



Scheme 7 Gold-catalyzed intramolecular coupling of alkene to conjugated enyne

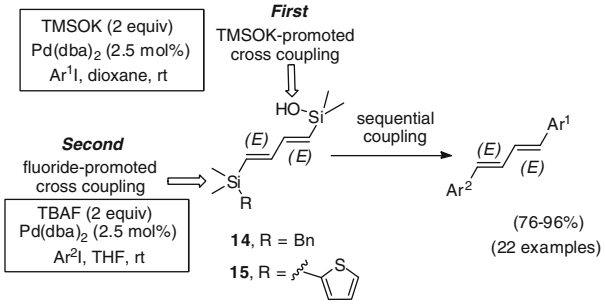
Additionally, this methodology was applied to the reductive coupling of 1,3-enynes to glyoxalates [13, 14], α-ketoesters [15], and heterocyclic aromatic aldehydes [16] and ketones as electrophiles. The use of chiral phosphines as ligand to the rhodium catalyst allowed the enantioselective version of these reactions to take place.

Au-Catalyzed Intramolecular Coupling of Alkenes to 1,3-Enynes

The intramolecular cyclization of alkene to conjugated enyne by Au(I) catalysis has been observed by Echavarren, the triple bond being activated by the cationic metal (Scheme 7) [17]. The obtained product features an exocyclic conjugated diene and the selectivity originated from the intramolecular attack of the olefin to the triple bond. In the process, a molecule of MeOH traps the cationic intermediate.

2.1.2 From Stereodefined 1,3-Dienes

The coupling of stereodefined and functionalized 1,3-dienes will be described in this section. Recent developments regarding the functionalization of the dienes in order to improve the scope of the coupling and the stability of the dienes will be detailed. Since the starting materials engaged are stereopure, the risk of isomerization under the conditions of the coupling has to be taken into consideration.



Scheme 8 1,4-Bissilylbutadienes for Pd-catalyzed cross-coupling reaction

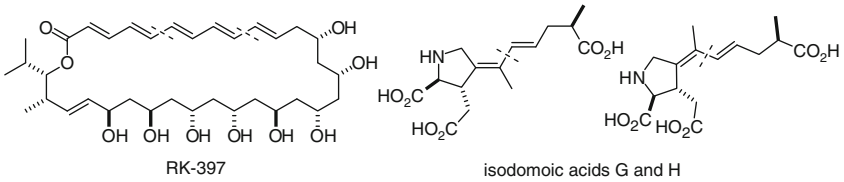
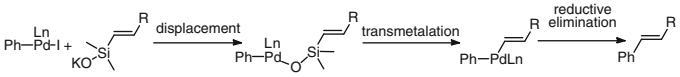


Fig. 3 Selected natural products and their synthetic disconnections for Pd-catalyzed cross-coupling

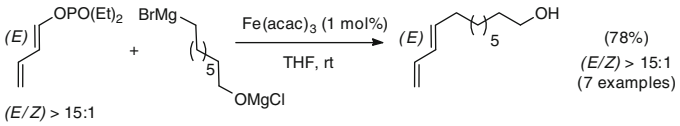
Pd-Catalyzed Cross-Coupling

Denmark devised the Pd-catalyzed sequential cross-coupling of (*E*,*E*)-1,4-bissilylbutadienes **14** to prepare unsymmetrical disubstituted (*E*,*E*)-dienes (Scheme 8) [18]. The strategy is based on the ability to perform the Hiyama–Denmark cross-coupling reaction at the two different sites under different conditions. Hence, the silanol reacted under basic activation (TMSOK) in the presence of $Pd(dba)_2$ with aryl iodides while the other silyl group is inert under these conditions. The second silyl group was activated in the presence of fluoride by addition of TBAF to promote the coupling with aryl iodides in the presence of $Pd(dba)_2$. For both reactions, a wide range of aryl iodides (electron rich or electron poor) were cleanly reacted with **14** to deliver unsymmetrical 1,4-diaryl (*E*,*E*)-1,3-dienes. Furthermore, the authors designed the bissilane **15** in which the 2-thienyl group replaces the benzyl appendage to perform the second coupling of Ar^2I more efficiently when the connected aryl (Ar^1) is electronically poor. The stereocontrolled synthesis of (*E*,*E*)-1,4-bissilylbutadienes **14** and **15** by hydrosilylation of alkynes is detailed in Sect. 4.

The methodology was also applied to the Pd-catalyzed cross-coupling of bissilane with vinyl iodides for the synthesis of the polyene chain of RK-397 in Fig. 3 [19]. When the regioselectivity of the reaction is not an issue, silanol can be activated by $TBAF{\cdot}8H_2O$ to promote the cross-coupling with vinyl iodide as illustrated during the syntheses of isodomoic acids [20]. It has to be stressed that



Scheme 9 Mechanism for the Pd-catalyzed cross-coupling of potassium silanolate to phenyl iodide



Scheme 10 Fe-catalyzed coupling of (*E*)-dienol phosphate with Grignard reagent

conversion of benzyl(dimethyl)vinylsilane into dimethylvinylsilanol can be carried out with TBAF·xH_2O and should therefore be avoided when regioselective couplings are intended.

The Pd-coupling between the potassium salt of silanolate (fluoride-free) and aryl iodide was the subject of mechanistic investigations by Denmark (Scheme 9) [21]. Kinetic, spectroscopic and synthesis experiences demonstrated that the transmetalation step occurs from a neutral tetracoordinate intermediate containing an Si–O–Pd bond formed by displacement of iodide. After the transmetalation step, a reductive elimination process provides the coupled adduct.

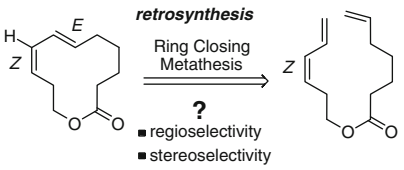
The methodology was extended to the Pd-catalyzed coupling between 1,1-alkene bissilane and vinyl iodide for the preparation of (*E*,*E*)-dienes bisaryls [22].

Fe-Catalyzed Coupling of Dienol Phosphates with Grignard Reagents

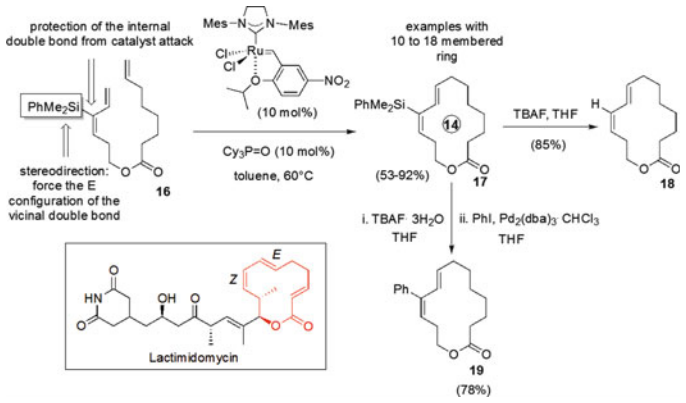
Cahiez described a new stereoselective route to prepare terminal conjugated dienes (Scheme 10) [23]. The cross-coupling of stereopure dienol phosphates and Grignard reagents catalyzed by $Fe(acac)_3$ allowed the expedient preparation of various alkyl terminal dienes. During the coupling, the dienol phosphate is not isomerized when reacted with alkyl Grignard reagents. On the other hand, partial isomerization occurred when aryl Grignard reagents were employed.

The dienol phosphates are known to be less reactive and more stable than the corresponding dienic iodides or bromides. However, under iron catalysis, the oxidative addition step is easier than with palladium or nickel catalysts. This methodology circumvents the conventional use of dienyl iodides or bromides. Since these reagents are known to be sensitive and prone to polymerization, this strategy constitutes a substantial improvement for the synthesis of stereodefined conjugated dienes.

The configuration of the phosphate being maintained during the process, it is crucial to have stereodefined dienol phosphates at one's disposal. The authors published an interesting and simple methodology for preparing the dienol phosphate in a diastereoselective manner, the details of which can be found in Sect. 4.



Scheme 11 Challenges associated to ring closing metathesis (RCM) of 1,3-dienic system



Scheme 12 Strategy for the RCM of 1,3-dienic system

Ru-Catalyzed Ring Closing Metathesis of 1,3-Dienic Systems

The ring closing metathesis (RCM) of conjugated diene for the formation of macrocycle is not a trivial task in regards to the stereoselectivity issue (Scheme 11). This is in stark contrast to the RCM of medium size rings in which the constraint of the ring imposes the configuration of the diene moiety, usually (*Z*/*Z*). Recently, Fürstner investigated the preparation of conjugated dienes incorporated into macrocycles (10–18 membered rings) by RCM [24]. To be successful, the strategy requires control of both the configuration and the regioselectivity of the newly formed double bond as well as discrimination of the two olefinic sites of the 1,3-diene group.

The authors unveiled a new strategy for the metathesis, based on the substitution of the 1,3-diene appendage by a bulky R_3Si group. This substituent directs the regioselectivity by protecting the internal alkene, and the stereoselectivity by exerting a steric effect in favor of the *E* isomer (Scheme 12). Hence, when compound **16** was treated with ruthenium carbene catalyst, the macrocycle **17** was obtained in good yield and selectivity. The reaction was exemplified with different ring sizes (10–18 membered rings). Note that the use of a catalytic amount of tricyclohexylphosphine oxide is mandatory to prevent the isomerization of the double bond before the ring closure. Next, the protodesilylation occurred smoothly in the presence of TBAF to afford the conjugated *E*,*Z*-diene **18**. Alternatively, the

silane moiety can be converted into silanol before pallado-catalyzed coupling with phenyl iodide to afford the trisubstituted conjugated diene **19**.

The stereodefined silyl-substituted diene was prepared by hydrosilylation of the corresponding conjugated enyne in the presence of platinum carbene complex (for details see Sect. 4).

This investigation culminated with the total synthesis of lactimidomycin, a macrolide containing the *E*,*Z*-conjugated diene motif.

Ring-closing metathesis (RCM) was also applied to the macrocyclization of 16-membered lactone core of plecomacrolides [25]. The reaction required the use of the robust second generation Grubbs catalyst under refluxing toluene. The stereochemistry of the process proved to be highly influenced by the functional groups present on the substrate.

2.1.3 From Stereodefined Alkenes

Pd-Catalyzed Cross-Coupling

The Pd-catalyzed coupling of stereodefined vinyl iodides and vinylzinc is a convenient method for the stereoselective construction of conjugated dienes. Among all the groups involved, the group of Negishi explored the Pd-catalyzed C–C bond formation between alkenyl iodides and vinylzinc or borane to obtain (*Z*,*Z*)- or (*Z*,*E*)-conjugated dienes (Scheme 13) [26].

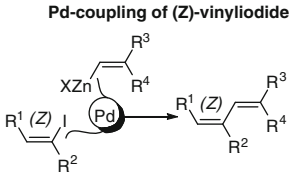
The strategy, which applies to the synthesis of several complex natural products, is documented in the recent Negishi's Nobel Lecture [27, 28].

2.1.4 From Alkynes

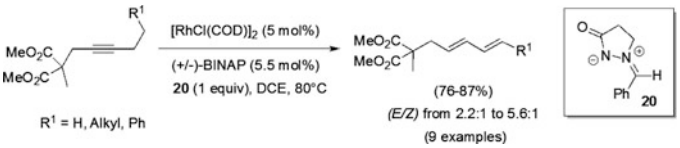
The strategies involving the use of alkynes for the preparation of conjugated dienes usually require more challenging stereocontrol of the double bonds generated during the reaction. The transition metal-catalyzed intramolecular coupling of 1,6-enynes, known as cycloisomerization, gives carbo- or heterocycles possessing a 1,3-diene group. Among the metals employed, palladium was the most exemplified. These methods are the focus of a recent review and will not be covered here [29].

Rh-Catalyzed Isomerization of Unactivated Alkynes

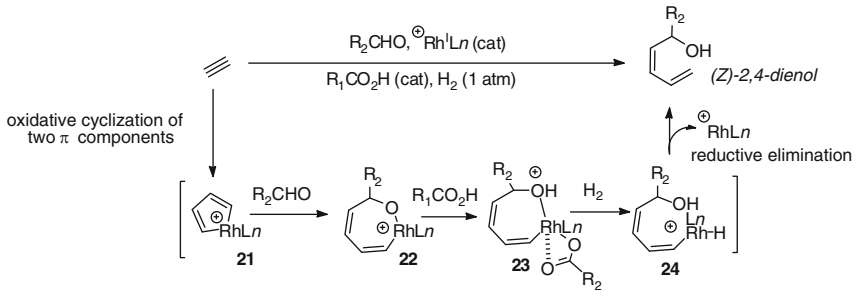
While the isomerization of activated (i.e., bearing electron-deficient groups) alkynes into 1,3-dienes is well documented, the challenging isomerization of non-activated alkynes into 1,3-enynes has been less investigated. In 2006, Hayashi reported the Rh-catalyzed isomerization of unactivated alkynes to conjugated dienes promoted by the azomethine imine reagent **20** (Scheme 14) [30]. Thus,



Scheme 13 Pd-catalyzed Negishi coupling



Scheme 14 Rh-catalyzed isomerization of unactivated alkynes



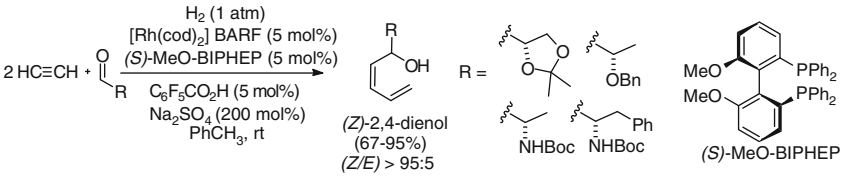
Scheme 15 General mechanism for the Rh-catalyzed reductive coupling of acetylene to carboxaldehydes

alkyl substituted alkynes were converted into the corresponding conjugated dienes with varying stereoselectivities (*E*/*Z* from 2.2:1 to 5.6:1). The exact contribution of **20** is unclear but the authors suspected it could play a role in the formation of rhodium hydride species, which in turn could promote the isomerization process.

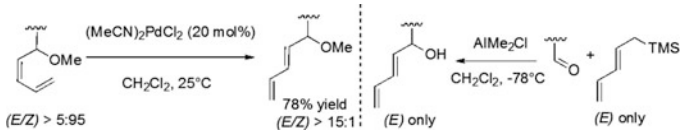
Rh-Catalyzed Reductive Coupling of Acetylene to Electrophiles

As an extension of the 1,3-enyne coupling, acetylene was directly coupled to electrophiles (i.e., carboxaldehydes and imines) in the presence of cationic rhodium catalyst and Brønsted acid as co-catalyst to provide (*Z*)-2,4-dienyl allylic alcohols or amines (Scheme 15). α-Ketoesters, activated aldehydes [31, 32], and *N*-arylsulfonylimine [33] were described as suitable electrophiles for the reductive coupling of acetylene delivering (*Z*)-dienyl allylic alcohols or amines in a stereocontrolled manner.

The mechanism postulated was supported by mass spectrometry, computational modeling, and insightful experiments [34]. As in the previous examples involving



Scheme 16 Reductive coupling of acetylene to chiral aldehydes



Scheme 17 Pd-catalyzed isomerization of (*Z*)-dienol ether and Sakurai reaction with 2,4-dienyltrimethylsilane

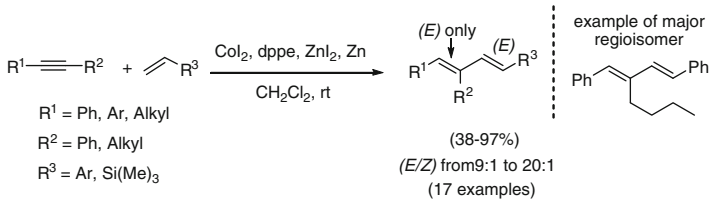
1,3-enynes, the catalytic cycle involves a prior oxidative cyclization of two molecules of acetylene with the rhodium catalyst to form the cationic rhodacyclopentadiene **21**. The insertion of the carbonyl group would convert **21** into the oxarhodacycloheptadiene **22**, which is too electron-deficient to tolerate the hydrogenolysis of the Rh–O bond. Possible prior protonation of the Rh–O bond of **21** by the Brønsted acid followed by its binding to the rhodium would enable the hydrogenolysis of the Rh–O bond and the dissociation of the carboxylic acid to form cationic hydride intermediate **24**. Consecutive reductive elimination of **24** would deliver the (*Z*)-2,4-dienol and the cationic Rh-catalyst. In some cases, chiral phosphine-containing catalysts enabled the formation of adducts with high enantioselectivity.

In the course of the investigation on the Rh-catalyzed reductive coupling of acetylene to α-chiral aldehydes, the authors noticed a good to excellent level of catalyst-directed diastereofacial selectivity for the conversion to (*Z*)-dienol adducts with diastereoselectivities ranging from 12:1 to 20:1 when carried out with (*S*)-MeO-BIPHEP (Scheme 16) [32].

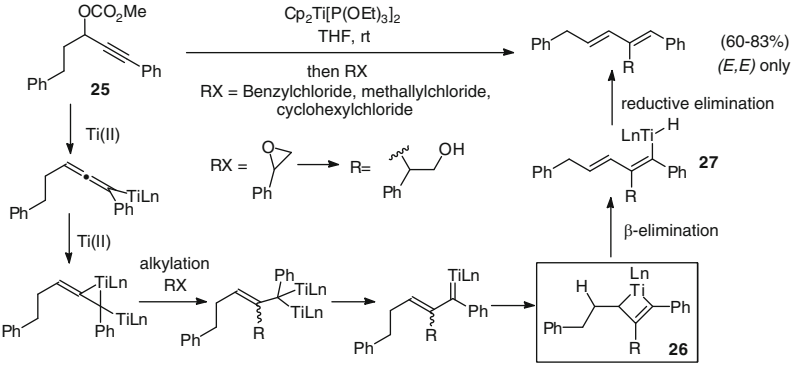
Further broadening the methodology, the conversion of a (*Z*)-2,4-dienyl ether into its (*E*)-isomer has been exemplified in the presence of Pd(II) (Scheme 17) [35]. Alternatively, the Sakurai reaction was employed by the same authors to convert stereoselectively 2,4-dienyl(trimethyl)silane and aldehyde into 2,4-dienol adducts in the presence of Lewis acid.

Direct Co-catalyzed Ene–Yne Coupling

The intermolecular coupling of alkyne and alkene is a straightforward solution for the preparation of conjugated dienes without prefunctionalization of reagents. Cheng recently described the use of Co(II) salts and ethylenebis(diphenylphosphine) (dppe)



Scheme 18 Co-catalyzed coupling of alkynes and alkenes



Scheme 19 Preparation of conjugated dienes by Ti-promoted alkylation of propargyl carbonate

in combination with Zn and ZnI_2 to perform the coupling between alkynes (1 equiv.) and alkenes (1.2 equiv.) and afford trisubstituted conjugated dienes (Scheme 18) [36]. The chemistry works particularly well when the alkynes are substituted with aromatic rings, giving the coupled adducts in best yields. The regioselectivity of the reaction was examined with unsymmetrical alkynes (R^1 = Ph, R^2 = Alkyl) and was found to reach a value of 9:1 in favor of the product possessing minored steric interactions between R^2 and the vinyl appendage.

The proposed mechanism involves the initial formation of Co(I) from Co(II) by reduction with Zn. Coordination of the alkyne and the alkene to Co(I) to form a metalocyclopentene intermediate could be followed by sequential β-hydride elimination/reductive elimination to provide the conjugated diene.

Ti(II)-Promoted Alkylation of Propargyl Carbonates

Takeda employed the Ti(II) reagent, $Cp_2Ti[P(OEt)_3]_2$, to perform the reductive titanation of γ-monosubstituted propargyl carbonate and to produce the substituted diene after treatment with an electrophile (Scheme 19) [37]. The attack of Ti-reagent on the propargyl carbonate **25** leads indirectly to the formation of titanacyclobutene **26**, a key intermediate for the stereoselective formation of the conjugated diene after β-elimination step and reductive elimination of **27**. Whereas

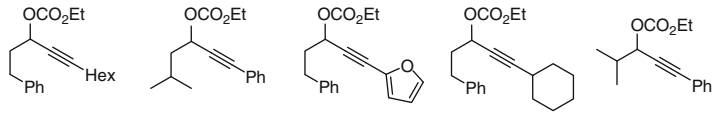
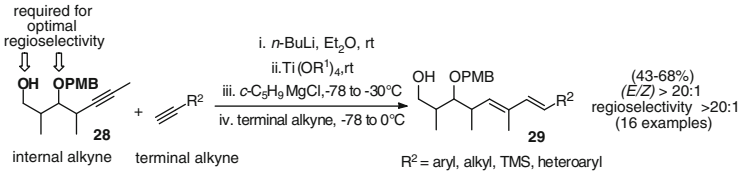


Fig. 4 Propargyl carbonates examined for the Ti-catalyzed coupling



Scheme 20 Cross-coupling of two alkynes

benzylchloride, methallyl chloride, and cyclohexylchloride were suitable electrophilic partners, delivering the conjugated dienes in 60–83% yields, benzyl bromide and *n*-butylchloride failed to afford the expected products. The use of an epoxide provided the primary carbinol after nucleophilic ring opening. Note that only the formation of (*E*,*E*)-conjugated dienes was observed by the authors.

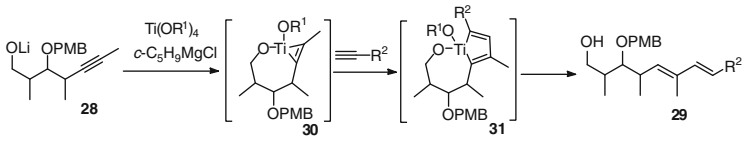
Various aryl or alkyl substitutions of the propargyl carbonate, shown in Fig. 4, were compatible with this chemistry, delivering the corresponding conjugated dienes in fair to good yields (36–73%) upon treatment with the aforementioned electrophiles.

The Ti(II)-promoted couplings of alkynes and vinyl sulfone [38] and vinyl pivalate [39] were also reported by Takeda.

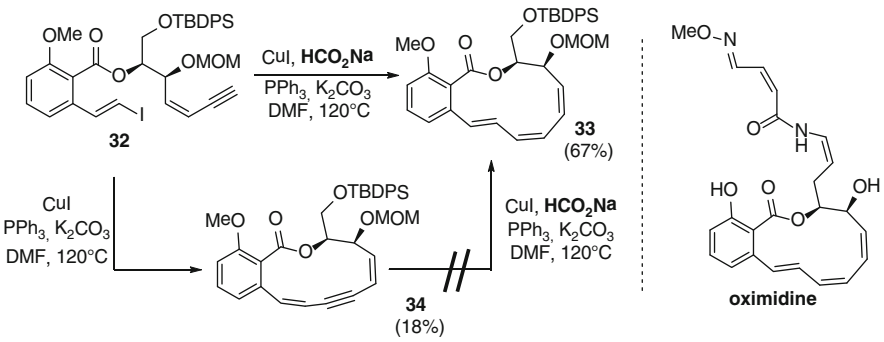
Ti(II)-Promoted and Directed Coupling of Alkynes

The cross-coupling of two alkynes is another direct route to 1,3-dienes. Micalizio reported a strategy in which the Ti-promoted one-pot coupling of an appropriately functionalized internal alkyne **28** with a terminal alkyne takes place regio- and stereoselectively (Scheme 20) [40]. In order to attain such levels of selectivity, the course of the reaction is directed by the hydroxyl group of the internal alkyne and to some extent to the OPMB group. The first step involves the deprotonation of the hydroxyl. Then sequential introductions of Ti(IV) and the Grignard reagent acting as reductant are followed by the addition of terminal alkyne substituted with alkyls or heterocyclic rings. This procedure resulted in the coupling of the two alkynes with total control of the regioselectivity and selectivity.

As depicted in Scheme 21, the regioselectivity observed in this coupling reaction can be rationalized by assuming that coordination of the titanium hydroxylate to the internal alkyne as in **30** could direct the course of the process. The insertion of the terminal alkyne according to a transition-state structure minimizing 1,2-steric interactions would afford the metalacyclopentadiene **31** then, after work-up, the coupled product **29**.



Scheme 21 Proposed intermediates



Scheme 22 Reductive ene–yne macrocyclization

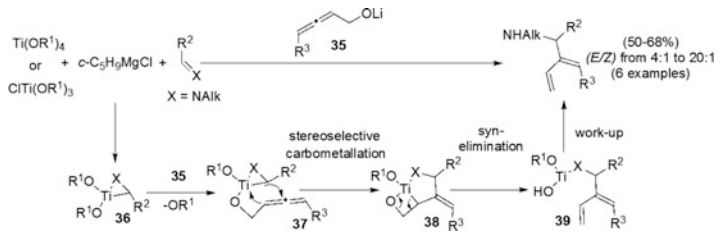
Cu-Promoted Coupling of Alkynes to Alkenyls Iodide

Georg reported recently the reductive alkyne–alkene coupling applied to the preparation of macrocyclic conjugated dienes or trienes (Scheme 22) [41]. The classical conditions of the Castro–Stephens coupling were applied but in the presence of sodium formate which allowed diene to be obtained instead of enyne. Hence, when compound **32** was treated with CuI/PPh_3/K_2CO_3 and HCO_2Na in DMF, the macrocycle **33** was formed as the sole (*E*,*Z*) isomer. Even though sodium formate has been identified as the source of hydride, the mechanism of the transformation does not involve a "simple" reduction of the possible enyne intermediate. Indeed, the enyne **34** is not reduced into the diene **33** in the conditions of the reaction. Eventually, the study culminated with the elegant synthesis of oximidine.

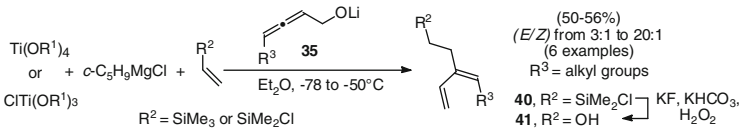
2.1.5 From Allenic Alcohols

Ti-Mediated Coupling of Allenic Alcohols with π-Components

The cross-coupling of allenic alcohols with π-components (i.e., imines, alkenes, alkynes) has also been investigated by Micalizio to prepare substituted 1,3-dienes bearing allylic amine functionality when reacted with imines (Scheme 23) [42]. The strategy is based on the reactivity of azatitanocyclopropanes **36** formed by



Scheme 23 Proposed mechanism



Scheme 24 Preparation of 1,3-dienes by Ti-promoted cross-coupling of vinylsilane and allenol

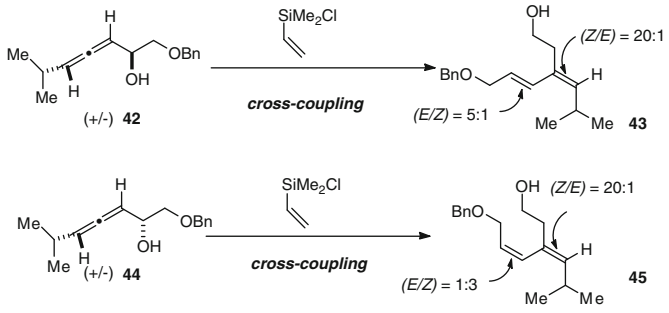
the reaction of Ti(IV) and Grignard reagent in the presence of π-components (i.e., imines). After a probable ligand exchange with **35** conducting to **37**, the intramolecular carbometalation of the allene moiety would lead to the metalaoxetane **38** which is expected to furnish the diene **39** according to the *syn*-elimination pathway.

The stereoselectivity of the reaction is highly dependent on the nature of R^3: when R^3 = Me, moderate selectivity was observed (*E*/*Z* = 4:1), whereas excellent results were obtained when R^3 = *i*-Pr (*E*/*Z* > 20:1).

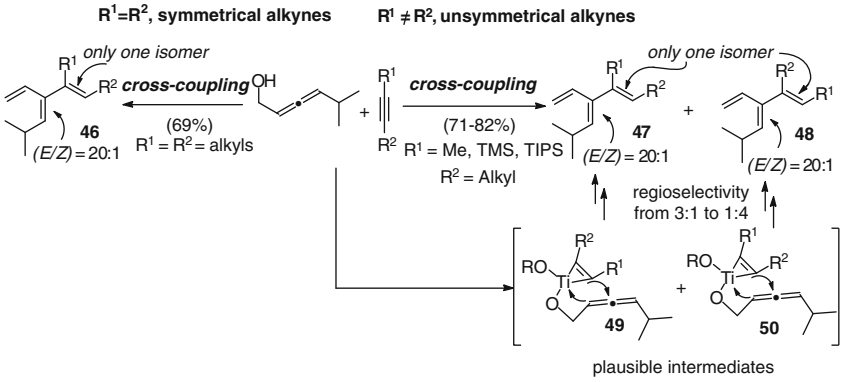
This methodology was later extended to the cross-coupling of vinylsilane and allenol (Scheme 24) allowing the preparation of conjugated dienes with high selectivities (*E*/*Z* = 20:1) [43].

Interestingly, the coupling of the lithium alkoxide of the allenol **35** and vinyldimethylchlorosilane delivering chlorosilane **40** was followed by oxidation of the σ_{C-Si} bond to afford the primary carbinol **41** in global yields ranging from 53% to 55%.

The stereocontrol of the reaction has also been investigated using stereodefined allenol for the coupling with vinyldimethylchlorosilane (Scheme 25). The reaction of **42** and **44**, described in Scheme 25, provided substituted 1,3-dienes **43** and **45** with varying levels of selectivity. While in both case the (*Z*)-trisubstituted olefin was obtained with high selectivity, the configuration of the second disubstituted olefin was secured with a moderate level of selectivity (*E*/*Z* = 5:1 to 1:3). Although the formation of the (*Z*)-trisubstituted olefin is consistent with a stereoselective *syn*-carbometalation, the formation of the disubstituted olefin is not stereospecific since the configuration of the hydroxyl group in the starting material is not completely directing the configuration of the double bond. As suggested by the



Scheme 25 Preparation of conjugated dienes from stereodefined allenol and vinylsilane



Scheme 26 Preparation of conjugated dienes by cross-coupling of allenol and alkynes

authors, the moderate level of selectivity observed could be explained by competition between *syn*- and *anti*-elimination of the organometallic intermediate.

Applied to substituted alkynes, the titanium-mediated cross-coupling of 1,3-disubstituted allenol delivered stereoselectively trienic products (Scheme 26) [44]. When the alkyne is symmetrically substituted ($R^1 = R^2$), only one regioisomer **46** is produced in 69% yield and the stereocontrol of the two olefins is very efficient (*E*/*Z* up to 20:1). When an unsymmetrical alkyne is engaged ($R^1 \neq R^2$), two regioisomers **47** and **48** may be expected according to the path of the attack of the titanocyclopropenes **49** and **50**. The regioselectivity of the reaction may be dictated by the steric hindrance of the substituent R^1 vs R^2 to reach a value of 3:1 (**47**/**48**) when R^1 = Me and R^2 = alkyl. Interestingly, the regioselectivity was reversed with silyl-substituted alkynes providing the coupled products with a regioselectivity of 1:4 (**47**/**48**) in 71–82% yields. In both cases, though, the selectivity reached the same level (*E*/*Z* up to 20:1). The disubstitution of the allenol is essential for the success of the transformation: monosubstituted allenols led to 1,4-dienes.

2.2 Transition Metal-Free Methods

While the stereocontrol of the transition metal-based preparations of conjugated dienes originates mainly from the ability of the metal to bind the π-components, electronic and steric effects usually dictate the stereoselectivity of transition metal-free methodologies. Some evolution of known methodologies and recent development in this field will be presented in the following section.

2.2.1 From Imines

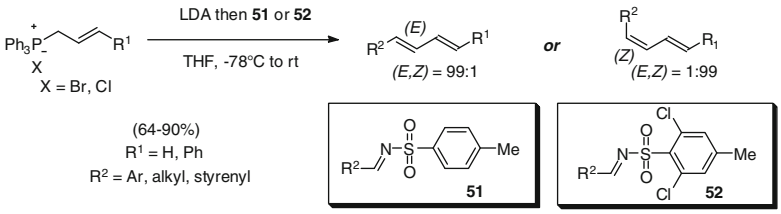
Tian developed a tunable stereoselective synthesis of conjugated dienes through the olefination of activated imines with semi-stabilized phosphonium ylides (Scheme 27) [45]. Based on the Wittig reaction, this strategy requires prior deprotonation of the phosphonium salt by a strong base for the formation of the ylide which acts as nucleophile. Whereas many modifications centered on the nucleophile of the Wittig reaction have been reported over the years, Tian unveiled a study based on the modification of the electrophiles employing imines. Hence, the use of a *p*-toluenesulfonyl group to activate the imine as in **51** resulted in the exclusive formation of (*E*,*E*)-dienes when the allylphosphonium was employed for the coupling in the presence of LDA. On the other hand, it was found that the 2,6-dichlorobenzenesulfonyl group activated the imine as in **52** and steered the selectivity of the reaction exclusively toward (*Z*,*E*)-diene production.

The methodology was exemplified with various substituted imines (R^2 = aryl, alkyl, styrenyl) allowing the stereodefined access to several substituted (*E*,*E*)- or (*Z*,*E*)-conjugated dienes in yields ranging from 64% to 90%.

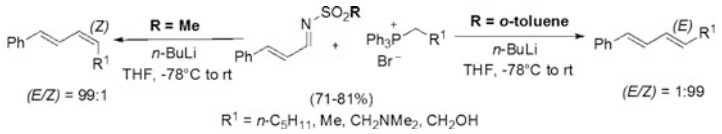
The coupling between activated imines and non-stabilized phosphonium ylides was studied next (Scheme 28) [46]. In this case, the (*E*)-selectivity was observed when the imine was activated with *o*-toluenesulfonyl group and treated with phosphonium ylides generated by action of *n*-BuLi. Interestingly, when a methanesulfonyl group activated the imine, the selectivity was reversed to produce the (*Z*)-isomer.

2.2.2 From Epoxide

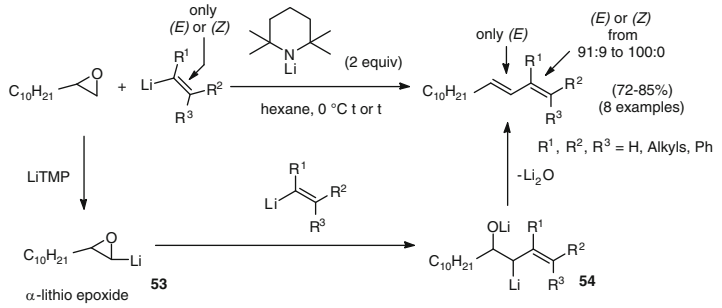
α-Lithiated epoxides are highly electrophilic species. Due to the ring strain of the epoxides and the important polarization of the Li–C–O bonds, α-lithiated epoxides **53** can suffer ring opening when exposed to alkenyllithiums leading to hydroxylate **54**, which β-eliminates Li_2O to form conjugated dienes (Scheme 29) [47]. Hodgson has illustrated this reactivity with 1,2-epoxidodecane and stereodefined alkenyllithiums for the stereoselective formation of conjugated dienes. After the deprotonation of the epoxide with LiTMP, the addition of the alkenyllithium to **53** occurred with almost total retention (from 91:9 to 100:0) of the configuration of



Scheme 27 Cross-coupling of imines and semi-stabilized phosphoniums



Scheme 28 Preparation of 1,3-dienes from imines and non-stabilized phosphoniums



Scheme 29 Condensation of 1,2-epoxidodecane and alkenyllithiums

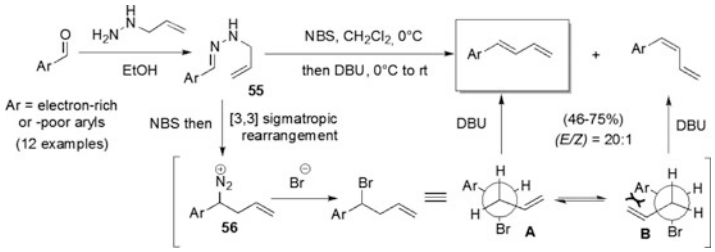
the double bond. Next, the *syn*-elimination of Li_2O afforded the (*E*)-olefin with an excellent control of the selectivity.

Recently, the stereoselective preparation of 1,3-dienes was described according to metal-free methodologies with reagents that are air and moisture insensitive.

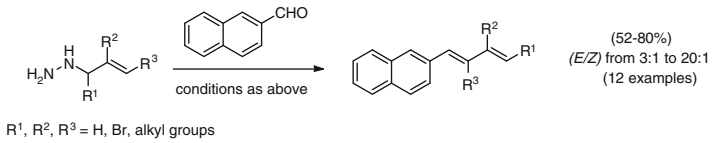
2.2.3 From *N*-Allylhydrazones

The strategy reported by Thomson relies on the [3,3] sigmatropic rearrangement of *N*-allylhydrazone initiated by a brominating agent such as NBS (Scheme 30) [48]. The one-flask procedure began with the formation of the hydrazone **55**, from aryl carboxaldehyde and *N*-allylhydrazine, followed by its sequential treatment with NBS and DBU as a base.

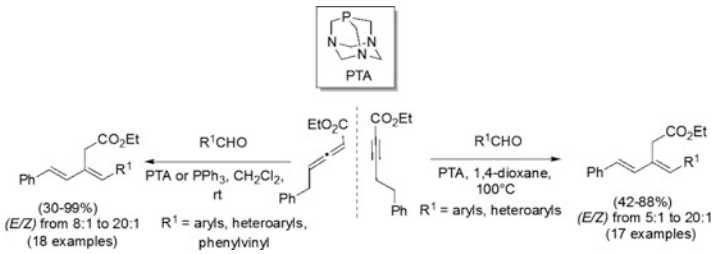
The mechanism involves probably the bromination of the hydrazone **55** followed by [3,3] sigmatropic rearrangement of the oxidized intermediate to furnish the



Scheme 30 One-flask transformations of carboxaldehydes to 1,3-dienes



Scheme 31 Preparation of polysubstituted 1,3-dienes



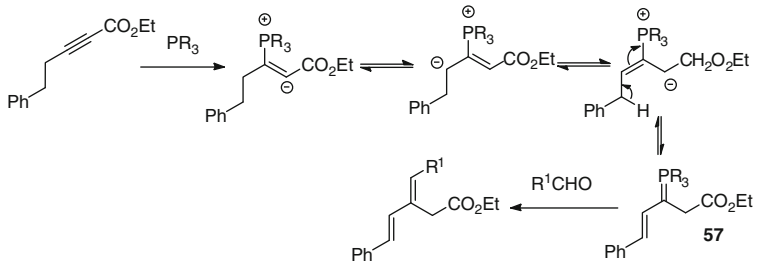
Scheme 32 Preparations of polysubstituted 1,3-dienes

diazonium **56**. Consecutive substitution at the benzylic position by bromide ion and DBU-mediated elimination of HBr would afford the conjugated diene. The formation of the (*E*)-isomer can be rationalized through an E2-mechanism of the conformer **A** presenting minor steric interactions compared to **B**.

Interestingly, the procedure was extended to substituted *N*-allylhydrazine to afford various polyfunctionalized conjugated dienes (Scheme 31).

2.2.4 From Allenoates and Alkynoates

Another strategy for the metal-free preparation of stereocontrolled bisaryl substituted 1,3-dienes relying on the conjugate addition of phosphine to allenoate was reported by He [49] and to alkynoates by Gothelf (Scheme 32) [50]. The strategy is inspired by the seminal work of Trost who described the isomerization of 2-alkynoate into conjugated dienes promoted by a catalytic amount of



Scheme 33 Proposed mechanism for the transformation of 2-alkynoate into conjugated dienes

triphenylphosphine [51]. The authors carried out the reactions with allenoate or 2-alkynoate and phosphine in the presence of an aldehyde as electrophile. It was anticipated that in situ generated phosphonium ylide would react with this aldehyde in a Wittig olefination reaction to furnish conjugated dienes. Triphenylphosphine and the phosphine 1,3,5-triaza-7-phosphaadamantane (PTA) were employed by He in CH_2Cl_2 at room temperature to promote the transformation of allenoate in conjugated diene. On the other hand, PTA in refluxing 1,4-dioxane gave the best result with 2-alkynoate as electrophile.

The mechanism for both methods is similar and has been proposed to begin with the conjugate addition of the phosphine to the Michael electrophile (i.e., allenoate or 2-alkynoate). In Scheme 33 the mechanism describing the transformation of 2-alkynoate is presented. After Michael addition, protons shift of the Michael adduct leads eventually to phosphonium ylide **57** that would react in a Wittig reaction with an aldehyde and displace the previous equilibria. Note that, despite the elevated temperature of the reaction with 2-alkynoate, no isomerization of the double bond allowing the conjugation of the ester with the double bonds was observed.

3 Dienes Substituted by Electron-Withdrawing Groups

Grafting an electron-withdrawing group onto a dienic structure has important consequences on its reactivity; therefore many methods have been proposed to access dienic esters, amides, nitriles, etc. The electron-deficiency induced on a diene not only reverses its behavior in cycloaddition reaction but also makes it a possible substrate for Michael additions. This well-known phenomenon has, for instance, been put into evidence in the recently isolated bioactive diterpenoid briareolate esters L–N where an (*E*,*Z*)-dienone motive acts as a reversible "spring-loaded" acceptor [52].

Here again an exhaustive review is impossible but significant examples among the recent developments are proposed in the following. Thus, selected illustrative examples have been gathered in four categories (couplings, isomerizations, metathesis, miscellaneous) presented herein. Note that the structure of the electron-attracting substituent and its position on the four carbons of the diene have been left undetermined.

3.1 Ene–Ene or Ene–Yne Couplings

Transition-metal-catalyzed cross-coupling reactions offer obvious solutions to design dienic scaffolds through carbon–carbon bond formation. The most commonly used catalytic organometallic reactions (e.g., Suzuki, Stille, Heck, Negishi) involve the coupling of two functionalized olefins. These widely employed methods are robust and relatively general in scope, warranting a good versatility. More recently, the direct coupling between simple alkenes and acrylates (or analogs) has also been developed. Alternatively, the palladium-catalyzed cross-couplings between alkenes and alkynes, the ene–yne couplings (also called intermolecular codimerization), offer attractive complementary solutions. The latter route has been the object of many developments lately, probably because it is based on the intramolecular enyne cycloisomerization (for review, see [53]), and resorts to unfunctionalized starting materials. It thus benefits from the advantages of simplicity and atom economy.

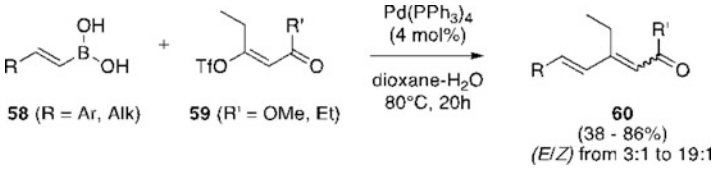
3.1.1 Functionalized Ene–Ene-Couplings

Palladium-catalyzed cross-coupling reactions have been largely employed in the synthesis of dienic structures. The very general Suzuki–Miyaura methodology has found a successful application in the stereoselective synthesis of ethyl substituted (*E*,*E*)-dienoic esters and dienones [54]. This coupling involved a series of vinylboronates **58** and vinyltriflates (or nonaflates) **59**, and led, in good yield, to the expected esters and ketones **60**. However, a partial isomerization of the electrophilic partner **59** occurred (Scheme 34).

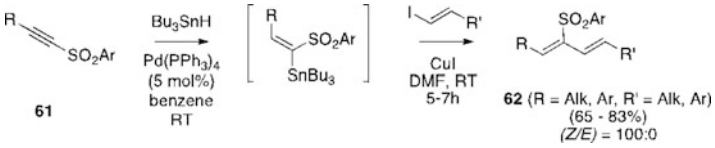
The Stille coupling, which also applies to dienes, is typically catalyzed by $Pd(PPh_3)_4$. Since the preliminary hydrostannylation of an alkyne such as **61** uses the same catalyst, a one-pot procedure was recently designed to access (*Z*,*E*)-2-arylsulfonyl-1,3-dienes **62** in good yields (Scheme 35) [55].

The Heck–Mizoroki coupling, which goes through a carbopalladation step, applies particularly well to electron-deficient alkenes that react even at room temperature [56]. A broad range of 1,3-dienes has been prepared from vinyl bromides and functionalized alkenes such as acrylates or enones [57]. Recent developments aim at involving functions sensitive to palladium catalysts or to tackle regioselectivity issues [58]. Thus, it was shown for instance that (*Z*)-iodoacrylates **64** could be assembled with hindered vinylboronates **63** to afford the borono dienic ester **65** (Scheme 36) [59, 60]. A side-reductive coupling of **64** into the (*Z*,*E*)-dienic diester **66** is observed that could be suppressed after optimization of the conditions [61].

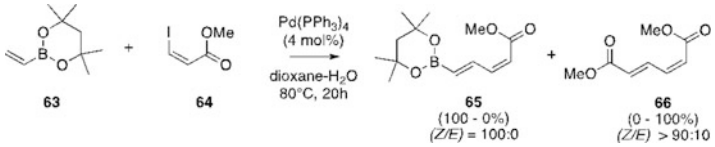
The problem associated with the 1,2-migration of the alkenyl-palladium intermediate when *gem*-disubstituted olefins are employed has also been addressed recently for vinylphosphate **67**. Elegant solutions have been found that rely on the modulation of the phosphine ligand and the amount of added LiCl (Scheme 37).



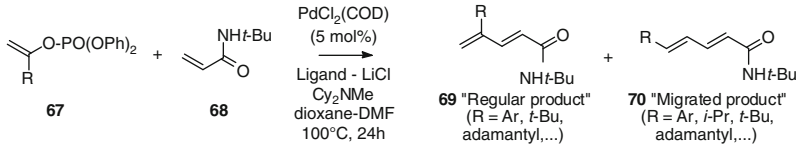
Scheme 34 Suzuki-coupling to access trisubstituted dienones



Scheme 35 Stille-coupling to access trisubstituted dienic sulfones



Scheme 36 Heck-coupling to access dienic esters

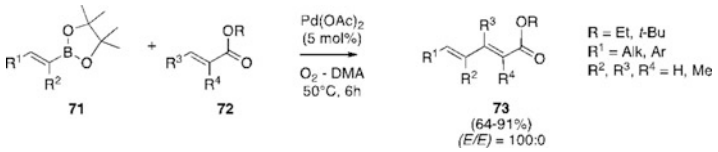


Scheme 37 Control of the regioselectivity in the Heck-coupling

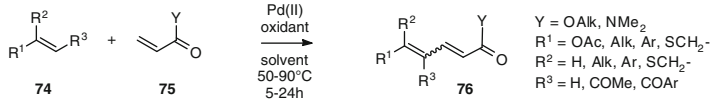
Thus, the expected ("regular") branched dienic amide **69** or its rearranged ("migrated") isomer **70** was obtained as desired [62].

A novel type of coupling was introduced in 2006 when Pd(II) was directly used under an atmosphere of dioxygen to perform oxidative Pd(II) catalysis [63]. This methodology, which connects alkenylboron derivatives **71** to olefins **72** (even highly substituted or cyclic ones) in the absence of base, works at moderate temperatures and in short times, minimizing undesired side-reactions. The dienic esters are recovered stereoselectively in good to high yields (Scheme 38).

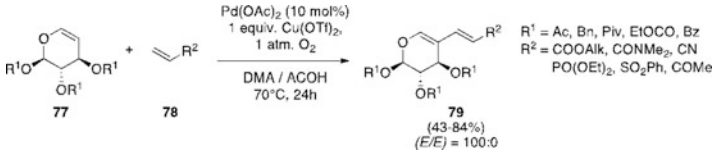
Some less classical coupling methodologies open complementary access to functionalized dienes. For instance, an alkyne hydrozirconation followed by a Pd-catalyzed alkenylation has been employed to prepare stereoselectively ethyl (*E*,*E*)-2-methyl-6-hydroxysorbate in excellent yield [64]. *N*-Vinyl-pyridinium



Scheme 38 Oxidative Pd(II) catalysis for coupling of vinylboronates



Scheme 39 Direct cross-coupling involving acrylates



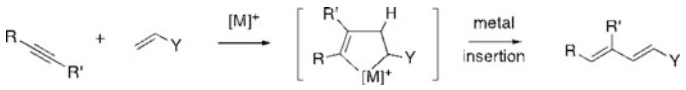
Scheme 40 Direct cross-coupling involving glucals and various activated olefins

tetrafluoroborate salts can also be employed as electrophilic coupling partners. Under palladium-catalysis conditions, they provide symmetrical (2*E*,4*E*)-1,6-dioxo-2,4-dienes in medium to good yields [65]. Very recently, a Pd(0)-catalyzed, Cu(I)-mediated methodology inspired from the Liebeskin–Srogl cross-coupling was described to connect α-oxo ketene dithioacetals with alkenylboronic acids [66]. It led to a series of aryl-substituted dienones in generally good yields.

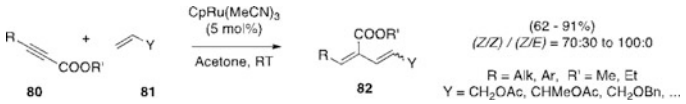
3.1.2 Direct Ene–Ene Couplings

Transition-metal-catalyzed cross-couplings through C–H bond activation of olefins have been under intense scrutiny lately as they open new routes to carbon–carbon bond formation. When applied to acrylates or acrylamides **75**, such a direct oxidative coupling affords dienes **76** in medium to good yields (Scheme 39). The catalytic system employed consists of Pd(II) derivatives in the presence of oxidants (such as $PMo_{11}VO_{40}$ [67] or CuX_2 [68] + O_2, AgOAc [69], etc.). Because it resorts to very simple precursors, this process is extremely attractive. However, its stereoselectivity still strongly depends on the substrate.

A synthetically useful application of this methodology to protected glucals **77** appeared recently (Scheme 40) [70]. It involves a variety of activated terminal olefins **78** and gives access to highly functionalized dienes **79**, ready for [4+2] cycloadditions, used for instance in the synthesis of natural products such as Olivin or Forsolin.



Scheme 41 Metalacyclopentene intermediate in the ene–yne couplings



Scheme 42 Examples of Ru-catalyzed ene–yne coupling

3.1.3 Ene–Yne-Couplings

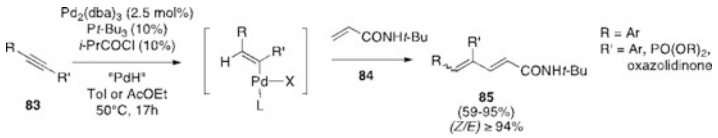
As for the direct alkene–alkene case mentioned above, the alkene–alkyne cross-couplings present the major advantage of involving simple non-functionalized partners and a catalytic amount of a transition metal complex. Note that these couplings are mechanistically distinct from metal carbene-mediated pathways (the enyne metathesis which also produces 1,3-dienes) (for review see [71]). Depending on the metal employed, the alkene–alkyne cross-couplings follow two different mechanistic pathways. Hence, electron deficient dienes have been prepared using Ti [72], Ni [73], Co [36], Rh [74], or Ru [75] (Ir has not been used for electron-deficient dienes to our knowledge). In all these cases, the formation of a metalacyclopentene resulted from a [2+2+1] cycloaddition, that involved, except for nickel, endocyclic β-hydrogen insertion (Scheme 41).

In general, an ester (or a carboxylate) is borne by the alkyne **80** (except for nickel where a second olefin inserts and extends the metallacycle) while the substituents on the olefin **81** vary a great deal, depending on the catalyst. Scheme 42 illustrates the synthetic utility of this coupling in the case of ruthenium catalysis [75]. Here, the dienes **82** are recovered regioselectively, the stereoselectivity depending on the olefin structure.

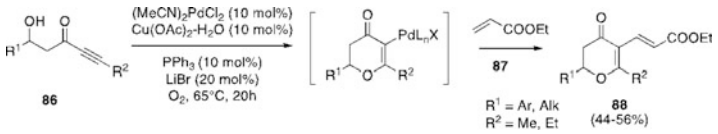
Note that a three-component version working in water and at room temperature has been reported [76]. It involves an arylboronic acid, an unactivated alkyne and methyl acrylate and is catalyzed by $Rh(OH)(COD)_2$ (4 mol%). It afford 3,4,4′-trisubstituted dienic esters in good yields and full stereoselectivity.

A totally different mechanism has been shown to apply to the palladium-catalyzed route. The speculated mechanism involves an in situ generated Pd(II)-H entity rather than a Pd(0) complex [77]. This hydride is supposed to add across the triple bond of the alkyne in a *syn* fashion, leading to a vinylpalladium intermediate that then behaves as in the classical Heck mechanism toward the olefin and affords the diene [78]. This methodology has allowed the transformation of acrylamide **84** into a series of dienamides **85** in good regio- and stereo-selectivities (Scheme 43).

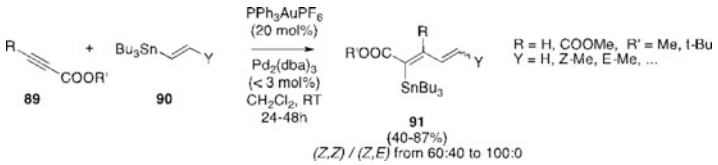
A somewhat related intramolecular oxy-carbopalladation reaction described for a series of hydroxy ynones **86** leads to a vinylpalladium intermediate that cannot undergo β-elimination and adds onto ethyl acrylate **87** (following a Pd(II)-catalyzed cascade Wacker–Heck reaction) to afford, stereoselectively, dihydropyranones **88** (Scheme 44) [79].



Scheme 43 Synthesis of dienamide by Pd-catalyzed ene–yne coupling



Scheme 44 Pd(II)-catalyzed cascade Wacker–Heck reaction



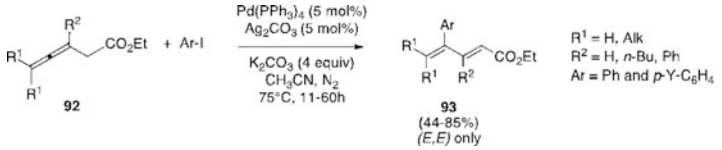
Scheme 45 Au-/Pd- cocatalyzed carbostannylation of substituted propiolates by vinylstannanes

Complementarily, a chloropalladation of the alkyne can be set using $PdCl_2$, and the resulting vinylpalladium chloride adds, in turn, on acrylates. Cholorodienic diesters are thus obtained provided $CuCl_2$ is added to the medium to re-oxidize the Pd(0) and close the catalytic cycle [80]. This reaction is further discussed in the section dedicated to halodienes (Sect. 5).

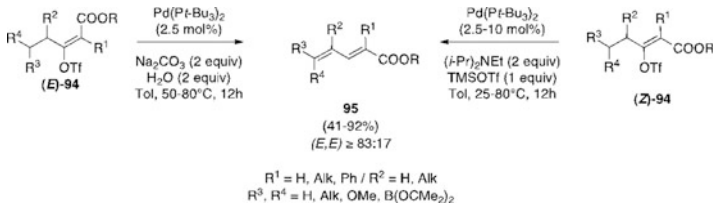
Let us close this section with a gold- and palladium-cocatalyzed carbostannylation of substituted propiolates **89** by vinylstannanes **90** (Scheme 45) [81]. The Au(I) electrophilic activation of the triple bond is said to promote the oxidative addition of the Pd(0) to the alkyne. Next, a transmetallation of the vinylstannane across one of the Pd–C bonds puts the reaction back on a Stille-type track. Several α-stannylated dienic esters such as **91** were thus prepared in medium to good yields. The stereocontrol is similar to that observed in the Stille coupling (high *syn* selectivity for the addition and stereospecificity with respect to the vinylstannane), albeit some stereochemical leakage was observed with bulky *Z*-stannanes.

3.2 Isomerizations and Rearrangements

The allenes and alkynes have the same oxidation state as 1,3-dienes. Therefore, they just require an adjustment of the oxidation level by internal hydrogen reorganization, a process that is obviously more atom economical than external sequential



Scheme 46 Isomerization of allenes by carbopalladation/β-H elimination



Scheme 47 Palladium-catalyzed elimination/isomerization of enol triflates

reduction-oxidation operations. The isomerization of alkynones [82, 83] and alkynoates [51, 84] into dienones and dienoates, respectively, has been studied for a while. Although transition metal catalysts have been the first to be proposed to promote these reactions, several recent examples show that organocatalytic approaches are also relevant.

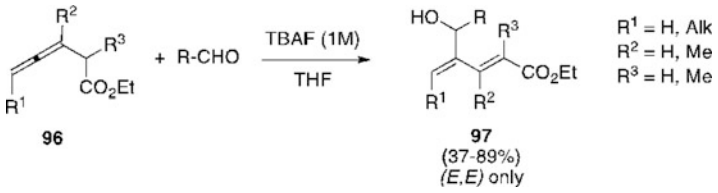
3.2.1 Isomerization of Allenes

The carbopalladation of allenes provides a convenient entry to π-allyl palladium species. In the presence of a non-conjugated ester group, such as in the 3,4-allenoates **92**, the β-H elimination transforms this intermediate stereoselectively into conjugated 1,3-dienes **93** incorporating di-, tri-, or even tetra-substituted double bonds (Scheme 46) [85].

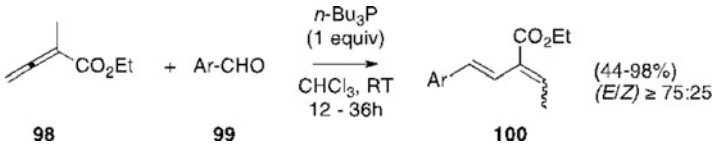
A recently described palladium-catalyzed elimination/isomerization of enol triflates is to be mentioned at this stage since it involves intermediate conjugated allenoates. This reaction is sensitive to the configuration of the starting enol triflate **94**, only the *E*-isomer being spontaneously transformed. However, addition of TMSOTf along with Hunig's base extends the reactivity to the *Z*-isomer (Scheme 47) [86]. The 1,3-dienic esters **95** are generally recovered in good yields and high to total stereoselectivity.

A simple base-induced tandem isomerization/hydroxyalkylation of the easily accessible 3,4-allenoates **96** has been described that furnishes, in a fully regio- and stereo-controlled manner, the expected dienic esters **97** (Scheme 48) [87]. The addition step involves an aldehyde but it can be extended to sulfonimines.

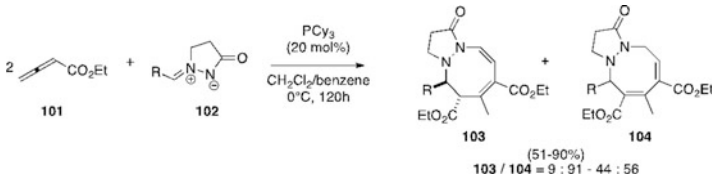
Complementarily, a similar isomerization/hydroxyalkylation sequence has been shown to isomerize the 2,3-allenoates into (*E*,*E*)-1,3-dienes. It is based on an organocatalytic process (reversible addition of phosphines in the 3-position of the



Scheme 48 Base-induced isomerization/hydroxyalkylation of β-allenoates



Scheme 49 Isomerization of a conjugated allenoate by tributylphosphine



Scheme 50 Phosphine-catalyzed [3 + 2 + 3] cycloadditions of azomethine imines with allenoates

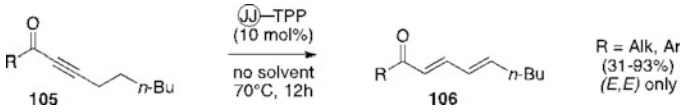
allenoate **98**) that generates a resonance-stabilized zwitterionic intermediate. The latter evolves by proton migration into an allylic phosphorus ylide that, in turn, undergoes a Wittig olefination toward aldehyde **99**, providing substituted dienes such as **100** (Scheme 49) [88, 89]. The conjugate character of the substrate explains that the regioselectivity of the aldolization step is the opposite to that in Scheme 48.

It has been shown very recently that replacing the aldehyde in the reaction above by azomethine imines **102** can lead, using PCy_3 as a catalyst in DCM/benzene (4:1) at 0 °C, to the incorporation of two allenoates **101** following a formal [3+2+3] cycloaddition process (Scheme 50) [90]. Thus, cyclic dienic esters are obtained as an equilibrating mixture of tautomers **103** and **104**.

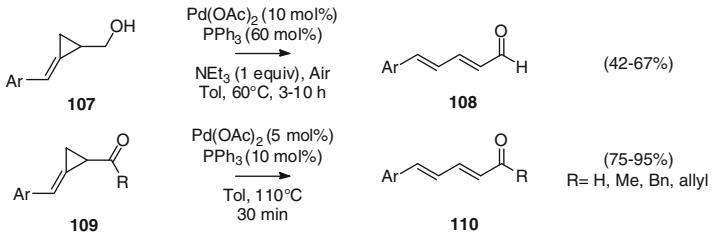
Another convenient isomerization process relies on an addition–elimination process in which NaI, LiBr, or LiCl react with an allenol [91]. The resulting product being a 2-methoxycarbonyl-3-halo-diene, this methodology will be detailed in the section dedicated to halodienes (Sect. 5).

3.2.2 Isomerization of Alkynes

As mentioned in the introduction, the isomerization of alkynoates into (*E*,*E*)-1,3-dienes is well-known [82–84]. Although organometallic routes have been the first



Scheme 51 Isomerization of alkynones by supported PPh_3 in solvent-free conditions



Scheme 52 Pd-catalyzed rearrangement of 2-benzylidenecylopropyl-carbinols and 2-benzylidenecylopropyl-ketones

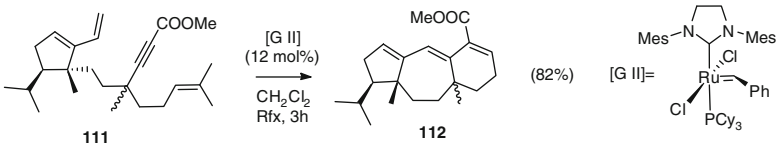
proposed for this reaction, they have been rapidly followed by phosphine-catalyzed processes, and the latter have gained momentum, as underlined in a review dedicated to the isomerization of alkynes [92]. Among the successive improvements listed in this paper, let us mention the use of phenol as a co-catalyst, of pentafluorophenol alkynoates as the activating group and the possibility to run the isomerization in water or the catalysis by polymer-supported phosphines. For instance, and in parallel to results obtained for the aza-Baylis–Hillman reaction, triphenylphosphine supported on *JandaJel* resin (JJ-TPP) has been shown to promote the efficient isomerization of a relatively large set of alkynones **105** in solvent-free conditions giving access to dienones **106** in medium to high yields (Scheme 51) [93].

More functionalized substrates have also been considered recently [94], giving, for instance, access to 5-alkoxy-2*E*,4*E*-dienones that are regarded as useful 1,4-disubstituted push-pull dienes.

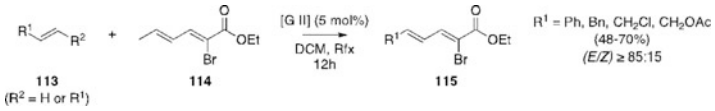
3.2.3 Rearrangements

The rearrangement of 2-benzylidenecylopropyl-carbinols **107** [95] or 2-benzylidenecylopropyl-ketones **109** [96] co-catalyzed by Pd(0) and Pd(II) has been shown to give access to (*E*,*E*)-2,4-dienals **108** and dienones **110**, respectively, in slightly different conditions (Scheme 52). A mechanism going through (*E*,*E*)-5-arylpenta-2,4-dien-1-ols has been proposed.

Finally, the spontaneous electrocyclic ring opening of pyran derivatives (obtained by a vinylogous aldol reaction between vinyl malononitriles and aldehydes) into dienamides is to be mentioned in this section [97].



Scheme 53 Tandem Ru-alkylidene catalyzed ring-closing metathesis to triene **112**



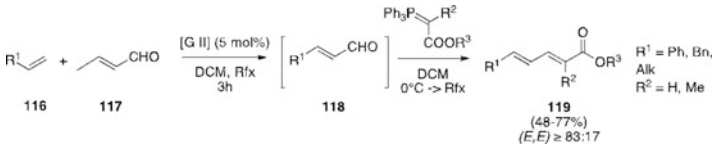
Scheme 54 Ru-alkylidene catalyzed metathesis of ethyl 2-bromosorbate and various olefins

3.3 Metathesis of Olefins

When applied to the synthesis of electron-withdrawing substituted conjugated dienes, metathesis presents the advantages of mild reaction conditions (and thus large functional groups tolerance), stability of the reagents and catalysts (such as ruthenium [98] or molybdenum [99, 100] alkylidenes), and availability of a wide range of olefin partners. The now classical RCM was for instance employed in a tandem version to assemble two of the three olefins and the alkynoate borne by substrate **111** to build up the [7.6.0] bicyclic core in **112** (Scheme 53) [101]. The tricyclic scaffold was used to complete the synthesis of guanacastepene A.

When it comes to dienes, metathesis is mainly used to scramble preexisting dienes with olefins, and this strategy applies particularly well to electron-deficient ones. Obviously, the issues regarding the chemo- and stereo-selectivities have to be considered with special care when involving dienes since only one double bond should react. A simple way to steer the regioselectivity consists in shielding one of the olefins by steric or electronic means. For instance, it was found that the deactivating effects of an ester group in addition to the influence of the bromine substituent in ethyl 2-bromosorbate **114** protected the double bond directly conjugated to the ester from cross-metathesis in the presence of Grubb's second generation catalyst [102]. Thus the reaction could be selectively directed toward the "remote" olefin and affords a variety of new 5-substituted dienic esters **115** with a high to total selectivity in favor of the (2*E*,4*E*) isomer (Scheme 54). Note that the carbonyl derivative can also be introduced via the olefin: 1,1-dibromo-1,3-pentadiene or even 3-methyl-1,3-pentadiene could be reacted, in similar conditions, with methyl acrylate or MVK, respectively, to afford products in which the metathesis occurred selectively on the less substituted olefin.

Interestingly, this approach applies to less stable (*Z*)-1,2-disubstituted alkenes and was successfully employed to access the (2*Z*,4*E*)-dienic fragment found in the dictyostatin family of anticancer molecules [103], or the *Z*-dienamide derived from the rearrangement of a Zincke salt [104]. Similarly, ethyl 2-methylsorbate was



Scheme 55 Sequence metathesis-olefination reaction to assemble dienes from three components

employed under analogous conditions to prepare the dienic moieties found in pinnaic acid and halichlorine [105]. Using a less active catalyst (Grubb's first generation for instance), ethyl 2*E*,4*E*-pentadienoate can be selectively reacted on its terminal double bond and combined with functionalized olefins to provide the expected dienic esters in excellent yield but medium stereoselectivity [106].

Another fruitful strategy relies on the combination of metathesis and non-metathesis reaction in a one-step sequence [107]. Here, the idea is to combine a terminal olefin **116** with an enal **117** through a regular metathesis step then trapping the resulting unsaturated aldehyde **118** in a Wittig reaction, yielding directly dienoate **119** (Scheme 55). It requires full chemical compatibility between the catalyst and reagents, demonstrated in the case of Grubb's II catalyst and phosphorus-based olefinating agents [108] (Wittig and Horner–Wadsworth–Emmons) and also diazoacetates [109].

3.4 Miscellaneous Reactions

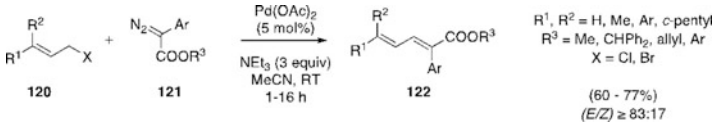
The presence of an electron-withdrawing group on the target structure explains that a relatively large series of miscellaneous reactions, often relying on stabilized ylides, could be used for the synthesis of these dienes.

The Pd-catalyzed condensation of allyl bromides or chlorides **120** on diazo ketones and esters **121** is probably one of the most convenient accesses to 2-aryl-dienone and 2-aryl-dienoate **122** [110]. The yields of this reaction are good and the selectivity high (Scheme 56).

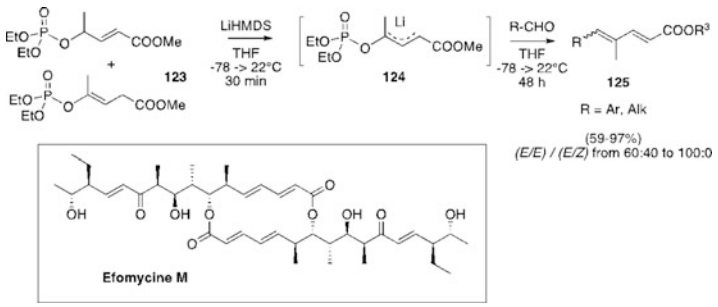
Other simple reagents for the rapid synthesis of conjugated dienic esters are the vinylogous Horner–Wadsworth–Emmons reagents, known for a while and employed for instance for a total synthesis of Efomycine M [111]. This family of reagents has recently been extended to branched allylic phosphonates such as **123**, opening up access to 4-methyldienoates **125** (Scheme 57) [112].

Note that the Still–Gennari olefination, well-known for its *Z*-selectivity, can be employed to transform the (*Z*)-enal **126** (itself resulting from a previous Still–Gennari step) into the (*Z*,*Z*)-dienoate **128**. This approach has been employed recently in a total synthesis of Archazolid A (Scheme 58) [113].

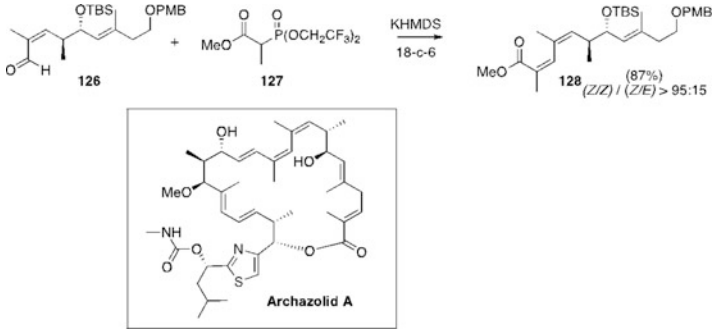
The ring-opening of arylpyridinium derivatives such as **129** in the presence of secondary amines provides 5-amino-penta-2,4-dienals better-known as the Zincke aldehydes. These dienals are useful synthons, explaining why this century-old reaction continues to find developments and applications in the synthesis of natural



Scheme 56 Pd(0)-catalyzed condensation of allyl halides on diazo esters



Scheme 57 Vinylogous Horner–Wadsworth–Emmons reaction with branched allylic phosphonates

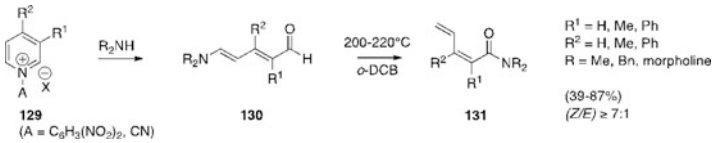


Scheme 58 Double Still-Gennari olefination to access an advanced synthon for Archazolid A

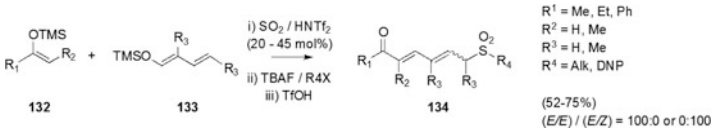
products such as norfuorocurarine [114] or porothramycins [115]. An unexpected thermal rearrangement of these Zincke aldehydes **130** led to the discovery of a selective route leading to *Z*-dienamides **131** in medium to good yields and stereoselectivities (Scheme 59) [104].

This rearrangement, of which the mechanism has been theoretically deciphered recently [116], can be followed by an intramolecular Diels–Alder cyclization, affording complex polycyclic lactams [117]. In relation to this pyridinium chemistry, the transformation undergone by pyridine *N*-oxides under the action of Grignard reagents is worth mentioning. It leads to substituted (*Z*)-dienal oximes in good yields [118].

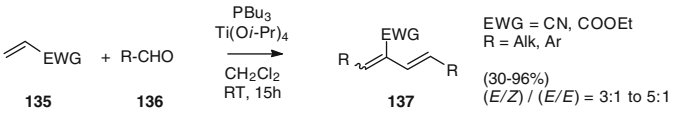
Another well-known category of reactions affording olefin and dienes consists of 1,2- and 1,4-eliminations. In recent applications to electron-deficient dienes, let us mention a four-component reaction that condenses 1-oxy-1,3-dienes **133**, silyl enol



Scheme 59 Thermal rearrangement of Zincke aldehydes into *Z*-dienamides



Scheme 60 One-pot, four-component transformation to dienones (DNP = 2,4-dinitrophenyl)



Scheme 61 Modification of the Morita–Baylis–Hillman reaction: an access to dienes

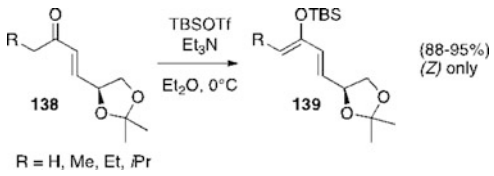
ethers **132**, SO_2 and electrophiles R^4X to furnish stereoselectively dienones **134** in good yields (Scheme 60) [119].

It has been shown recently that the condensation of an allylsilane, of which a double bond is conjugated to an amide (silylacrylamide), onto aldehydes in the presence of TBSOTf and NEt_3 gives direct access to dienamides after a β-elimination on the intermediate aldol product [120]. Another paper based on a Knoevenagel condensation involves β-diketones or β-ketoesters and enals. Proline catalysis leads to the expected conjugated dienones in good yields and after short reaction times [121].

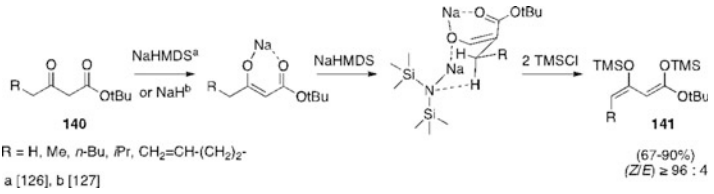
Another condensation–elimination sequence consists in a modification of the Morita–Baylis–Hillman reaction which provides dienes bearing an electron-withdrawing group (cyano or ester) in the 2-position **137** (Scheme 61) [122]. Its mechanism begins as in a classical Morita reaction; but a 1,2-proton shift occurs before the elimination of the phosphonium, leading to an intermediate ylide that condenses readily on a second aldehyde molecule.

4 Stereoselective Preparation of Heterosubstituted Conjugated Dienes

In this section, some recent representative processes allowing the stereoselective synthesis of hetero-substituted 1,3-dienes are described. They include access to chalcogeno dienes such as nitrogenated, phosphono, oxygenated, thio, or seleno



Scheme 62 Silylation of enone



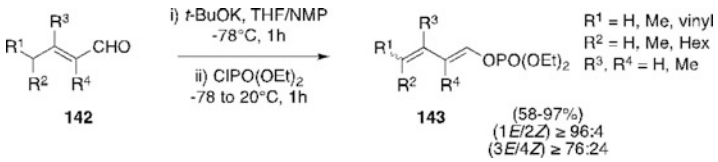
Scheme 63 Preparation of *tert*-butyl (1*Z*,3*E*)-1,3-bis(TMS)dienol ethers

substituted dienes, as well as metallo dienes such as silylated, stannylated, or borylated compounds. Worthy of note are the recent reviews that deal with the synthesis of silylated and borylated 1,3-dienes [123, 124].

4.1 From Enolizable Carbonylated Compounds

The synthesis of oxygenated dienes from methylcarbonyl compounds via formation of dienolates is a well established method that has been used recently to access 1,3-dienes bearing silyloxy, alkyloxy, or phosphate substituents in position 2 of the 1,3-dienyl motif. Wessjohann has reported the efficient synthesis of silyloxy-1,3-dienes starting from the corresponding enones using a classical method involving triethylamine as base and a silyltrifluoromethylsulfonate as electrophile. No racemization of the chiral dioxolane moiety borne by the substrate was observed under these smooth conditions (Scheme 62) [125].

The preparation of 1,3-bissilyloxyketene acetals from β-ketoesters has been largely described in the literature [126] and can sometimes be tedious due to the inherent reactivity of these bisdienol ethers. A preparative method has recently been described by Tanabe [127]. Starting from *tert*-butyl ketoesters and using sodium bis(trimethylsilyl)amide (NaHMDS) (2 equiv.) as base in cyclopentylmethylester, the reaction proceeds efficiently at 0–25 °C and leads to the *quasi* exclusive formation of the (1*Z*,3*E*) diastereomer (d.r. $\geq$ 96:4). The authors propose the approach depicted in Scheme 63, which minimizes the steric repulsions between the disodium dienolate anion and the TMS groups of the amide, to account for the good stereoselectivity of the transformation. In 2009, this practical method has been improved in terms of cost efficiency by replacing the exclusive use of NaHMDS as base (2.4 equiv.) by a combined use of NaH/NaHMDS (1.4 equiv.:1.4 equiv.) [128].



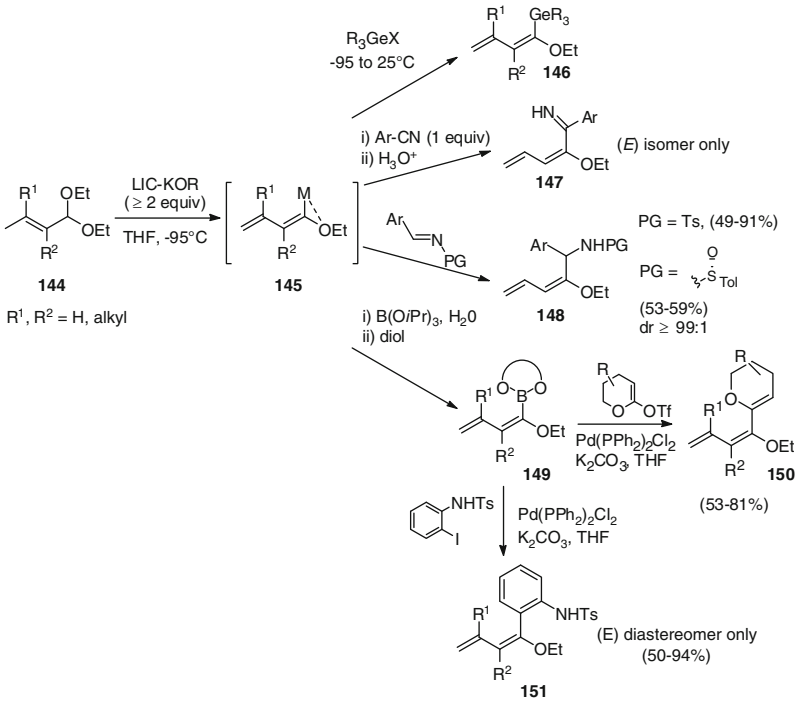
Scheme 64 Stereoselective preparation of dienol phosphates

O-Protection of dienolates derived from α,β-unsaturated carbonyl compounds is also a well-established method for the preparation of conjugated dienes featuring an oxygenated group in position 1 of the 1,3-dienyl moiety, even if the stereoselectivity of this process is often unsatisfactory. Dienol phosphates constitute good candidates for coupling reactions with organometallics and are thus useful for the synthesis of different types of conjugated dienes [23]. Stereoselective synthesis of dienol phosphates from α,β-unsaturated aldehydes has been recently reported by Cahiez [129]. Crucial to the control of the E_{C1-C2} diastereoselectivity is the use of potassium *tert*-butylate as base and the presence of *N*-methylpyrrolidinone (NMP) in the medium during the enolization step (Scheme 64).

1,3-Dienamines are usually prepared by condensation of secondary amines with α,β- or β,γ-unsaturated aldehydes or ketones [130]. Recently, transient formation of dienamine species by interaction of chiral amines with γ-enolizable α,β-unsaturated aldehydes has been largely explored and has been shown to be a powerful tool in organic synthesis [131, 132]. As the aminodienic compounds thereby generated are not isolated but further functionalized in situ, their synthesis will not be described here.

4.2 Elimination Reactions

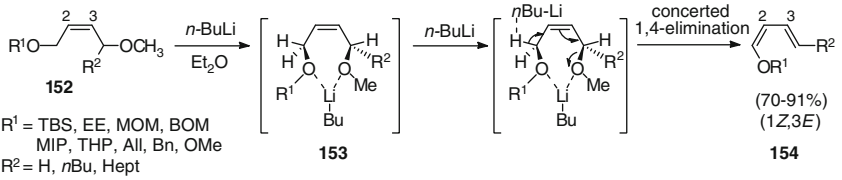
1,4-Elimination reactions on α,β-unsaturated acetals have been widely studied in the literature since the 1980s and have become a conventional method for accessing 1-alkoxydienes [133, 134]. Prandi, Venturello, and Deagostino have described a series of papers showing the large scope of this methodology, allowing the synthesis of differently substituted 1-alkoxydienes. They had previously shown that lithium/potassium mixed base (LIC-KOR) promotes the conversion of α,β-unsaturated acetals **144** into 1-alkoxydienes, inducing a 1,4-elimination reaction that is initiated by a metalation reaction occurring at the γ-allylic position. The elimination product can be further selectively metalated at the α-position when an excess of base is employed (at least 2 equiv.). The nucleophilic vinylmetal species thereby generated **145** can then be quenched with electrophiles, yielding the corresponding 1-susbstituted-1-alkoxydienes (Scheme 65). In the last 6 years, electrophiles such as halotriorganogermanes have been successfully used to access dienylgermanes **146** as pure (1*Z*) diastereomers [135]. When reacted with 1 equiv. of arylnitrile, the reaction with **145** leads to the selective formation of imines **147** as (*E*) isomers



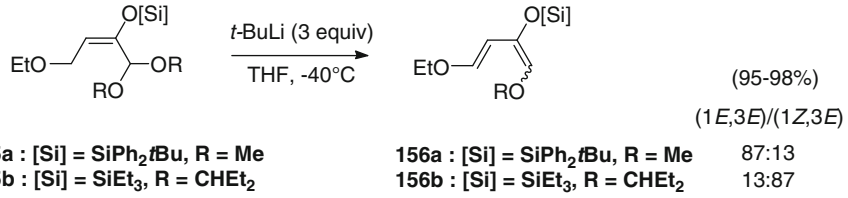
Scheme 65 Synthesis of differently substituted 1-alkoxydienes by metalation and quenching of α,β-unsaturated acetals

[136]. Quenching the same vinylmetallic species with imines furnishes the corresponding dienyl amines **148**. The use of electron-withdrawing substituents such as tosyl groups on the nitrogen atom of the imine leads to better yields [137]. Chiral *N*-sulfinyl imines can also be successfully employed and have been shown to furnish the expected dienes in a completely diastereosective way [138]. Alternatively, **145** can be efficiently trapped as a boronate derivative **149** when quenched with triisopropylborate and further esterified. These boronates can be coupled, via palladium catalyzed cross-coupling reactions, with lactone derived vinyl triflates to generate trienic compounds **150** [139, 140], or aryl iodides to yield the corresponding 1-aryl-1-alkoxydienes **151** [141].

The conversion of (*Z*)-1,4-dialkoxy-but-2-enes or (*Z*)-1,4-dialkylthio-but-2-enes into the corresponding 1-alkoxydienes or 1-alkylthiodienes was reported long ago, using sodium amide in liquid nitrogen or mixed metal bases (LIDAKOR) [142, 143]. Maddaluno had shown later that, when 1,1,4-trialkoxybut-2-enes were involved in the process, the simpler use of alkyllithium bases (*n*-BuLi at −40 °C or *t*-BuLi at −78 °C) could promote the 1,4-elimination reaction and allow the stereoselective generation of (1*Z*,3*E*)-1,4-dioxygenated or 1-alkylthio-4-alkoxy1,3-dienes [144, 145]. Recently, Tayama has reported similar 1,4-elimination reactions, starting from



Scheme 66 1,4-Elimination reaction of bisallylic ethers leading to (1*Z*,3*E*)-1-alkoxydienes



Scheme 67 Synthesis of 1,2,4-trioxygenated 1,3-dienes

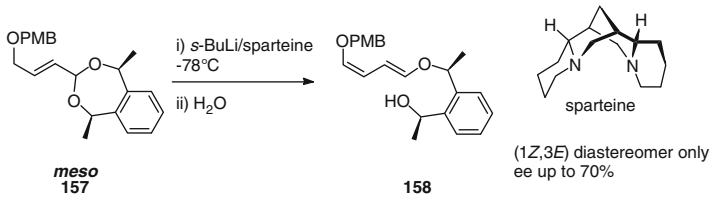
(*Z*)-bisallyloxyalkenes (Scheme 66) [146–148]. In some cases, the use of diethylether as a weakly coordinating solvent proved crucial for the stereoselectivity. When an alkyl substituent is present on the C2 carbon atom, the stereoselectivity of the process remains high. In contrast, C3 substituted substrates lead to mixtures of isomers.

The 1,4-elimination reaction can be performed with pyruvic aldehyde dimethylacetals, thus allowing the synthesis of 1,2,4-trioxygenated 1,3-dienes (Scheme 67). The stereoselectivity of the process in this case is mainly influenced by the size of the group on the acetal moiety [149].

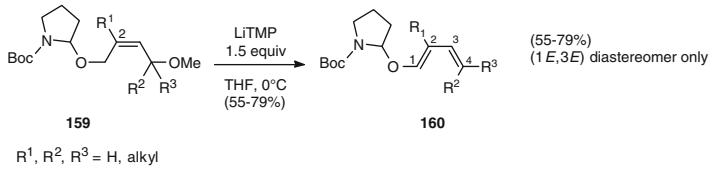
The possible enantioselective desymmetrization of a *meso*-allylic acetal by such 1,4-elimination reaction has been reported recently, using *s*-BuLi associated to sparteine. The reaction allows, in this case, the synthesis of a chiral (1*Z*,3*E*)-dialkoxydiene **158** (Scheme 68) [150].

When performing the 1,4-elimination reaction on *O*-(*N*-Boc-2-pyrrolidinyl) derivatives **159**, a reversal of the C1=C2 stereoselectivity of the diene was observed, leading to the exclusive formation of the (1*E*,3*E*) diastereomer (Scheme 69). In this case, the reaction required the use of an amide as base and the yields were highest when lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF was employed [151]. A significant drop of the yield is observed when an alkyl substituent is present on position C2 of the substrate.

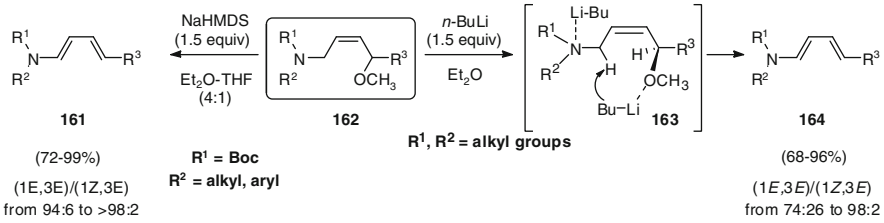
1-Aminodienes had been accessed in a similar way in the literature [152]. Recently, Tayama reported an analogous approach starting from (*Z*)-1-amino-4-methoxyalkenes [153]. When the nitrogen atom is substituted by two alkyl groups, the reaction can be performed in diethylether using *n*-BuLi as base and affords the corresponding 1-aminodiene **164** with generally high (1*E*,3*E*) stereoselectivity ((1*E*,3*E*)/(1*Z*,3*E*) from 87:13 to 98:2). The *Z* configuration of the initial alkenyl substrate proved essential to the stereoselectivity and formation of complex **163** is



Scheme 68 Desymmetrization of *meso* acetals by 1,4-elimination reaction



Scheme 69 1,4-Elimination reaction of bisallylic ethers leading to (1*E*,3*E*)-1-alkoxydienes



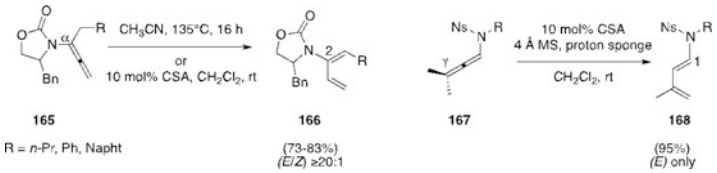
Scheme 70 Formation of aminodienes via 1,4-elimination reactions

proposed to explain the observed results (Scheme 70). When applied to the *N*-Boc derivatives, the use of NaHMDS as base proved superior to *n*-BuLi for both yields and stereoselectivities of the diene formation.

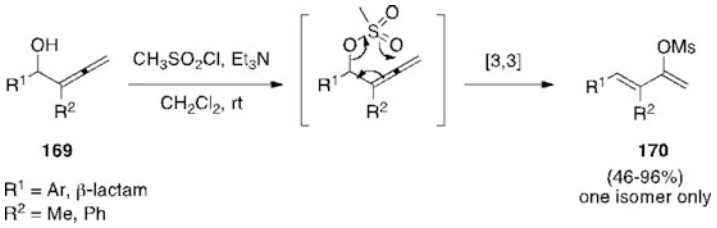
4.3 Isomerization Reactions

4.3.1 Isomerization of Allenic Compounds

Isomerization reactions of allenamides into amido dienes have been recently reported by Hsung [154, 155]. Depending on the allenyl substrate structure, regioselective α- or γ-isomerization can take place under acidic conditions (catalytic camphor sulfonic acid) or thermal activation (135°C), furnishing the



Scheme 71 Isomerization of allenamides into 1-amido or 2-amido-1,3-dienes



Scheme 72 [3,3] Sigmatropic rearrangement of α-allenol derivatives into 2-oxygenated dienes

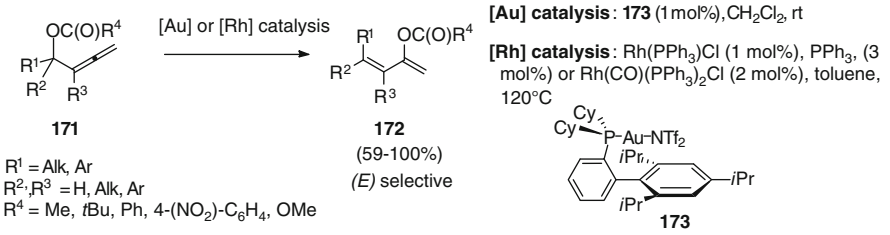
corresponding 2-amido or 1-amido diene in high yields (Scheme 71). The stereoselectivity of these processes is high, delivering, in each case, the *E* isomer exclusively. The amido dienes generated by such method can either be isolated or engaged in situ in further transformations, such as Diels–Alder reactions.

α-Allenic sulfonates can be easily transformed into 2-oxygenated 1,3-dienes through a [3,3] sigmatropic rearrangement (Scheme 72). The methylsulfonate substrate is formed in situ from the α-allenol under the smooth reaction conditions required for the global transformation that do not involve any metal salts nor expensive reagents. A total *E*-diastereoselectivity is observed in each reported case [156].

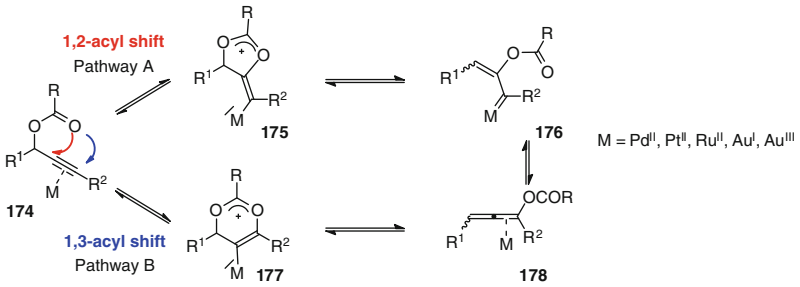
Recently, allenyl carbinol esters have also been efficiently rearranged into buta-1,3-dien-2-ol esters via metal catalyzed transformations. Gold (I) catalysis has proven efficient under smooth conditions (CH_2Cl_2 at room temperature) when using the biphenylphosphine-based catalyst **173**. The stereoselectivity of the process depends on the substrate and favors the formation of the *E* isomer (Scheme 73) [157]. More recently, the use of rhodium catalysts in similar transformations has been reported to lead to higher *E* selectivities, although in harsher reaction conditions (Toluene at 120 °C) (Scheme 73) [158].

4.3.2 Isomerization of Propargylic Esters

Metal complexes such as Pd(II), Pt(II), Ru(II), Au(I), or Au(III) have been reported to activate efficiently propargyl carboxylic esters to form complexes **174**, that evolve toward 1,2- and/or 1,3-acyloxy migration ([3,3] rearrangement) to generate



Scheme 73 Metal catalyzed isomerization of allenyl carbinol esters into buta-1,3-dien-2-ol esters



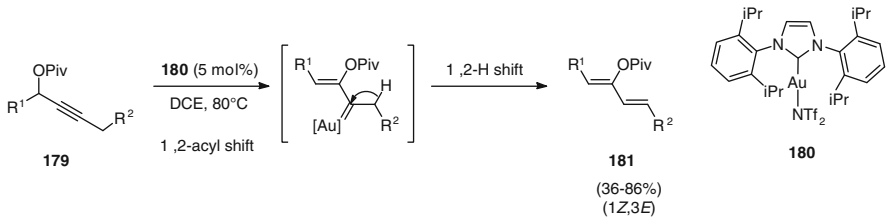
Scheme 74 Possible 1,2- and 1,3-acyl shift pathways

vinyl carbene metal species **176** or allenyl acetates **178**, respectively (Scheme 74). It is widely accepted that terminal or electron deficient alkynes preferentially react via pathway A while internal alkynes prefer pathway B. The intermediate species generated by such methods further react to lead to different products, including carbonyloxy 1,3-dienes (see below).

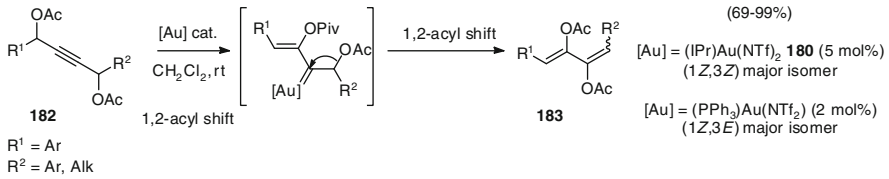
Through 1,2-Acyl Shift (Reactions Involving Vinyl Carbenoid **176**)

Lee has reported that the presence of an electron-withdrawing alkoxy group at the propargylic position could induce a preferential 1,2-acyl shift [159]. In the presence of platinum chloride ($PtCl_2$), the vinyl carbenoid is then prone to a 1,2-H shift reaction, providing an access to 1,3-oxygenated 1,3-dienes with a generally poor *Z*/*E* stereoselectivity. Isomerization reaction involving internal alkynes should lead to a 1,3-acyl shift pathway. Zhang has however observed a reversal in the 1,2- vs 1,3-acyl shift processes using $IPrAuNTf_2$ **180** as catalyst [160]. In this case, reactions with pivaloyl propargylic esters furnish 2-pivaloyloxy buta-1,3-dienes through 1,2-acyl migration followed by 1,2-H shift (Scheme 75). In most cases, formation of the (1*Z*,3*E*) isomer was obtained as pure stereoisomer.

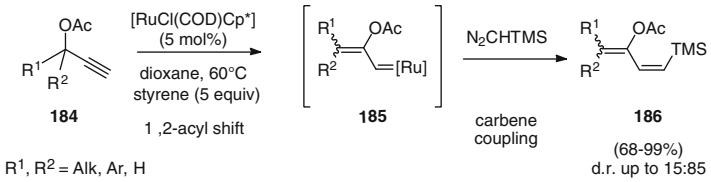
Starting from 1,4-bis(propargylacetates), a selective process involving two consecutive 1,2-acyl shifts occurs, affording the 1,3-bis(acetoxy)-1,3-dienes [161]. The stereoselectivity of the process depends mainly on the nature of the catalyst ligands. Involvement of $IPrAu(NTf)_2$ **180** favors the formation of the (1*Z*,3*Z*) isomer, while



Scheme 75 1,2-Acyl shift followed by 1,2-H shift



Scheme 76 Two consecutive 1,2-acyl shifts



Scheme 77 1,2-Acyl shift followed by diazoalkane carbene coupling

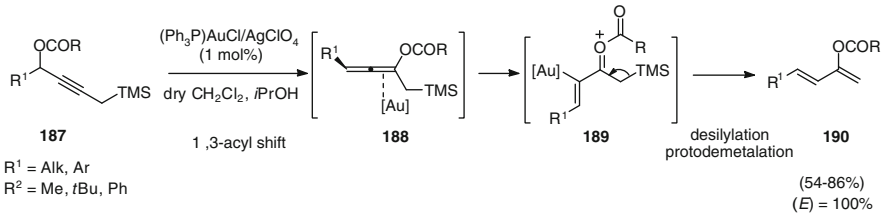
the more cationic $(Ph_3P)Au(NTf)_2$ leads to the major formation of the (1*Z*,3*E*) isomer (Scheme 76).

Interestingly, Dixneuf has shown recently that vinyl metal carbenoid intermediate **176** generated with an electrophilic ruthenium catalyst [RuCl(cod)Cp*] (Cp* = C_5Me_5) could be trapped by a diazoalkane carbene to yield acetoxy dienes **186** through carbene dimerization, in good yields (Scheme 77) [162]. No dimerization product and no cyclopropane formation could be noticed even when the reaction was run in the beneficial presence of 5 equiv. of styrene.

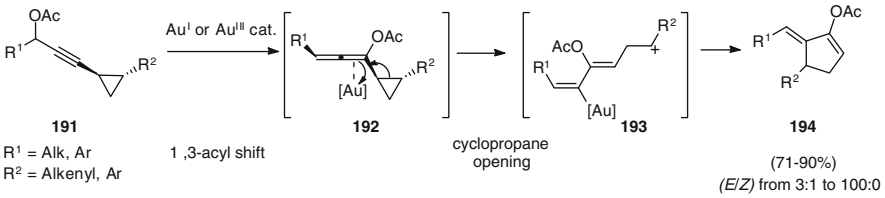
Ohe has described the trapping of the carbenoid intermediate **176** with heteroaromatic compounds such as furans or thiophenes [163–165]. Such sequences lead to the formation of heterosubstituted trienes, which are beyond the scope of this review.

Through 1,3-Acyl Shift ([3,3] Rearrangement)

1,3-Acyl shift isomerizations are generally observed when propargylic esters bearing an internal alkyne moiety are involved in the process. Zhang has reported that



Scheme 78 1,3-Acyl shift followed by desilylation process



Scheme 79 1,3-Acyl shift followed by cyclopropane opening and cyclization

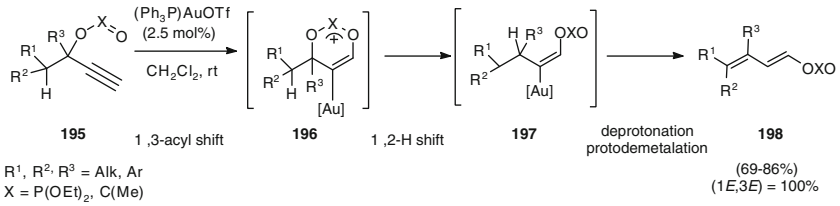
when propargylic esters are reacted in the presence of a catalyst such as $(PPh_3)AuCl$ associated with silver perchlorate, the expected [3,3] rearrangement occurred, leading to the formation of carboxy allenes such as **178**. In this case where the allene bears a trimethylsilylmethylene group, formation of an oxocarbenium intermediate **189** is observed. The latter is prone to desilylation and furnishes, after protodemetalation, the 2-acyloxy 1,3-diene **190**. This process offers efficient access to dienes with high *E*-selectivity of the non-enolic double bond (Scheme 78) [166].

In the case where the initial propargylic ester bears a cyclopropyl group, the formation of the allene intermediate **192** is followed by ring opening of the three-membered ring to lead to the cation **193** that cyclizes into alkylidene cyclopentenyl acetates **194** (Scheme 79) [167].

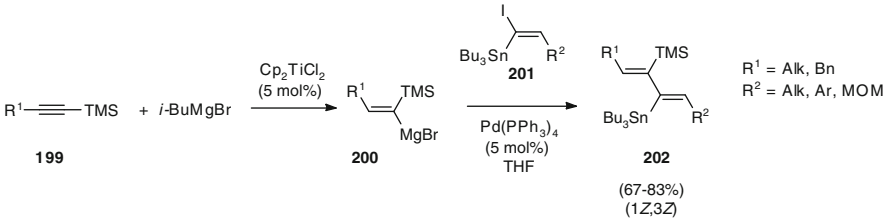
Stereoselective synthesis of 1-oxygenated dienes, starting from propargylic esters, has been reported with gold catalysts [168]. In this case, a 1,2-H shift on cyclic intermediate **196** allows the formation of a vinyl gold intermediate **197**, which, upon protodemetalation, furnishes the (1*E*,3*E*) diene **198** (Scheme 80).

4.4 Other Transition Metal Catalyzed Reactions

Transition metal catalyzed reactions and in particular cross-couplings are commonly employed to access conjugated dienes. Recently, efforts have been devoted to the stereoselective synthesis of silylated, stannylated, or nitrogenated 1,3-dienes using such methods.



Scheme 80 1,3-Acyl shift followed by 1,2-H shift



Scheme 81 Ene–ene palladium-catalyzed cross-coupling reaction

4.4.1 Ene–Ene Coupling Reactions

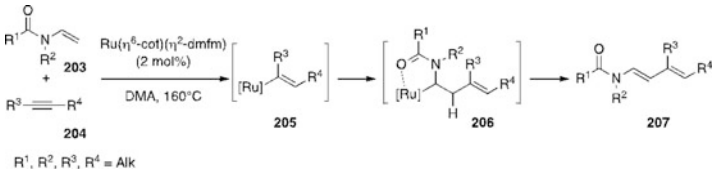
One significant advantage of these coupling reactions lies in the preservation of the initial alkenes stereochemistry in most cases, thus leading to highly stereoselective processes. (1*Z*,3*E*)-2-Silylated dienes have been synthesized by Cai through cross-coupling of (*E*)-α-halovinylsilanes with (*E*)-alkenylzirconium complexes in the presence of $Pd(PPh_3)_4$ catalyst [169]. Similarly, coupling of stereodefined α-silylvinylmagnesium **200** with α-iodovinylstannanes **201** leads to the formation of (1*Z*,3*Z*) difunctionalized 1,3-dienes **202** containing silicon and tin (Scheme 81) [170].

This methodology appears quite general to synthesize differently substituted conjugate dienes and has been recently applied to the stereoselective synthesis of chiral 2-sulfinylated dienes via the Stille process [171], or nitrogenated dienes via Suzuki [172, 173] or Negishi cross-coupling reactions for instance [174, 175].

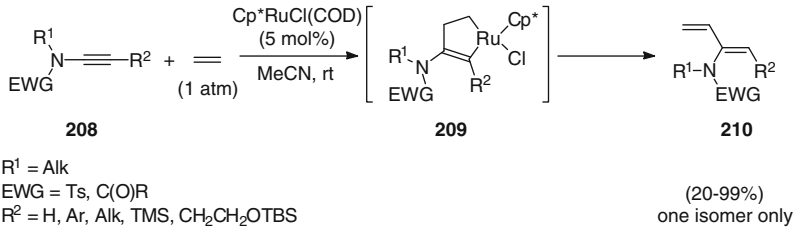
4.4.2 Ene–Yne Coupling Reactions

Ura and Kondo have recently reported the ruthenium-catalyzed co-dimerization of *N*-vinylamides with alkynes. The process leads to the formation of 1-amido-1,3-dienes **207** with a preferential (1*E*,3*E*)-selectivity. The authors proposed a mechanism involving the insertion of the alkyne into an Ru–H bond (generated in situ), leading to complex **205**, followed by a chelation assisted insertion of *N*-vinylamide into the Ru–C bond and subsequent β-hydride elimination (Scheme 82) [176].

In a complementary manner, the regioselective coupling of ynamides and ethylene has been reported to be mediated by a low valent ruthenium catalyst (Cp*RuCl(cod)). The formation of a ruthenacyclopentene **209** where the ruthenium



Scheme 82 Coupling of enamides with alkynes



Scheme 83 Coupling of ynamides with ethylene

lies in β of the nitrogen atom is proposed and explains the high regio- and stereoselectivities of the process, that leads, after β-hydride elimination and reductive elimination, to the formation of 2-nitrogenated dienes **210** (Scheme 83) [177].

4.4.3 Yne–Yne Coupling Reactions

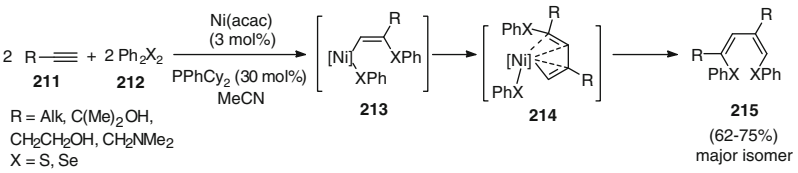
Nickel catalyzed addition of diphenyldichalcogenides (S and Se) on alkynes have been shown to produce 1,4-dichalcogenodienes **215**. The formation of complex **214** can account for the stereoselectivity of the process (Scheme 84) [178].

Cobalt-mediated stereoselective assembly of 1-dienamides has also been described by Vollhardt recently. The process involves a hydroaminative alkyne coupling of α,ω-diynes and leads to a completely *Z*-selective formation of the diene moiety with a regiochemistry that depends on the substrate [179].

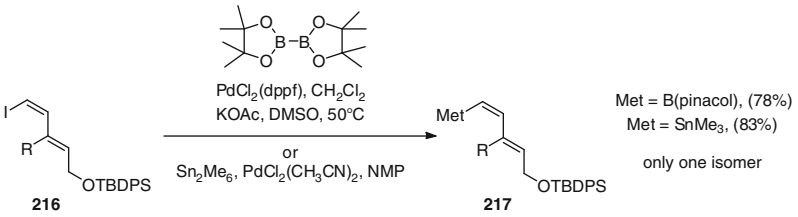
4.4.4 Other Transition Metal Catalyzed Reactions

Palladium catalyzed coupling reactions between halodienes and bis(pinacolato) diborane or hexamethylditin have been reported to yield the corresponding (1*Z*,3*E*)-1,3-dienyl boronate and stannane, respectively (Scheme 85) [180].

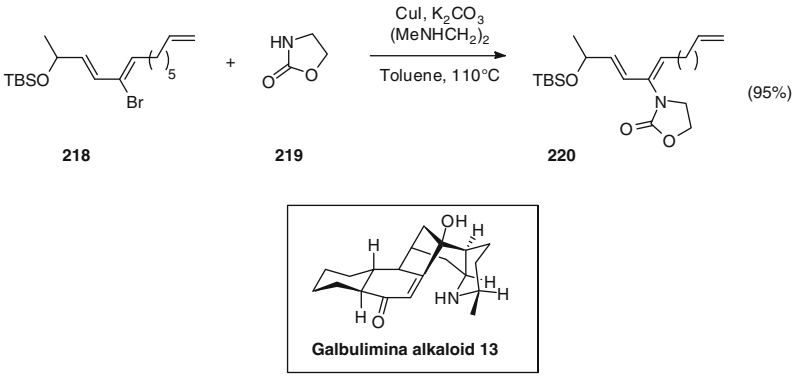
2-Amido diene motifs can be accessed by coupling reactions involving a halodiene and an amide. Movassaghi has, for instance, successfully applied this



Scheme 84 Addition of diphenyldichalcogenides on alkynes



Scheme 85 Palladium catalyzed coupling of iododiene and boron or tin

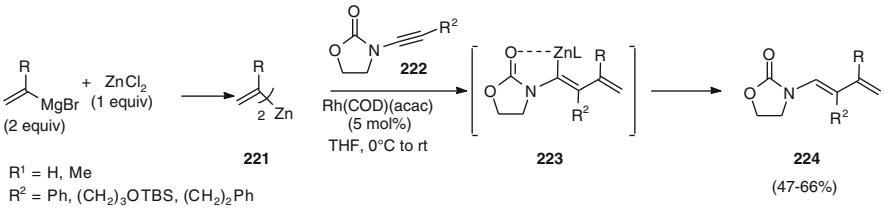


Scheme 86 Copper-catalyzed coupling of bromodiene and amide

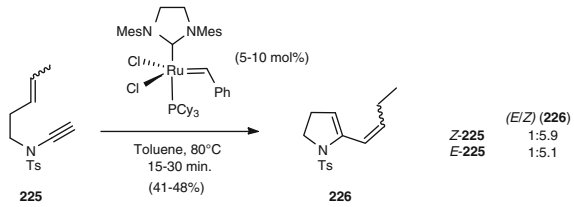
strategy in a copper-catalyzed coupling reaction in the course of the total synthesis of Galbulimina alkaloid 13 (Scheme 86) [181].

Interestingly, Lam has described a synthesis of enamides via rhodium-catalyzed carbozincation of ynamides [175]. When applied to dialkenylzinc compounds, this reaction leads to the regio- and stereoselective formation of 1-amidodienes **224** (Scheme 87). The regioselectivity of the reaction was explained by the possible formation of a chelated complex **223**.

RCM of an ene-ynamide substrate has been reported by Mori and Sato, using a second-generation ruthenium carbene catalyst. The process generates cyclic dienamides with a preferential *Z* configuration of the non-cyclic double bond (Scheme 88) [182].



Scheme 87 Carbozincation of ynamides



Scheme 88 RCM of ene-ynamide

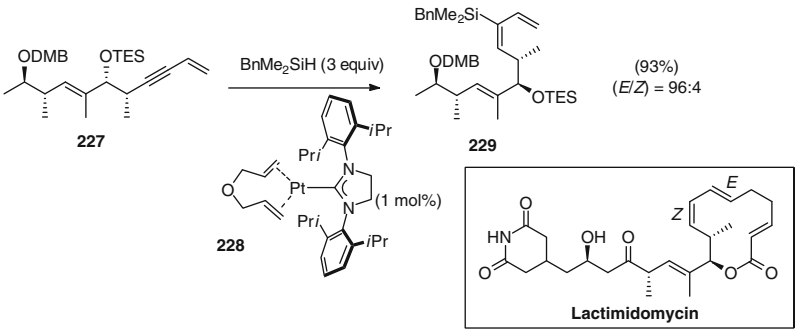
4.5 Hydrofunctionalization of Alkynes

Hydrosilylation, hydroboration, and hydrophosphination of conjugated enynes have been recently employed to access silylated, borylated, or phosphonylated 1,3-dienes with high stereoselectivities.

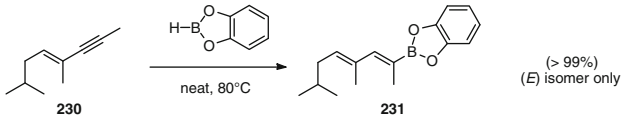
4.5.1 Hydrosilylation

Hydrosilylation of alkynes has been intensively studied, but the same reaction has barely been applied to the hydrosilylation of conjugated enynes. This reaction has however been reported to be catalyzed by platinum carbene complexes in the supporting information of a paper by Denmark describing the synthesis of unsymmetrical 1,4-disubstituted 1,3-butadienes [18]. In the reported examples, addition of dimethylalkoxysilane on a terminal enyne already bearing an aryl/benzyldimethylsilyl substituent at the vinylic terminus allowed the stereoselective formation of (*E*,*E*)-dienic silanols and thus the differentiation of the two silyl groups in the subsequent coupling reactions.

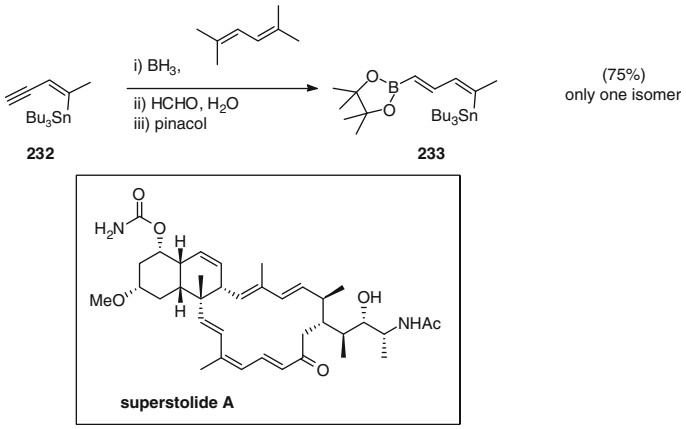
More recently, Fürstner has described the hydrosilylation of internal enyne compound **227** to be catalyzed by platinum carbene complex **228** (Scheme 89) [24]. The corresponding silylated diene **229** is thus efficiently obtained in a regio- and stereocontrolled way, en route to lactimidomycin.



Scheme 89 Platinum carbene catalyzed hydrosilylation of enyne



Scheme 90 Non-catalyzed hydroboration of enyne

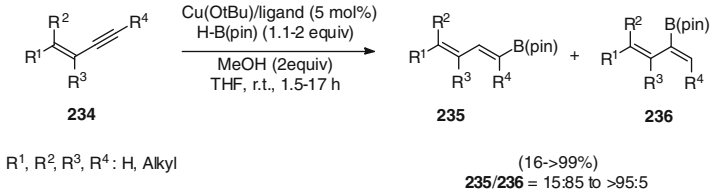


Scheme 91 Non-catalyzed hydroboration of ene–yne

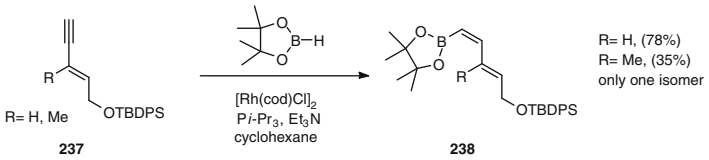
4.5.2 Hydroboration

Compared to the hydroboration of alkynes, the preparation of polyconjugated hydrocarbon compounds by hydroboration is still challenging both for transition metal- or non-transition metal-catalyzed processes. Moses has reported the clean conversion of enyne **230** into boronate **231**, as a single diastereoisomer, when using freshly distilled catecholborane (Scheme 90) [183].

Hydroboration of enyne has also been reported using the conditions developed by Snieckus to introduce cleanly a vinyl boronate moiety with complete (*E*) diastereoselectivity (Scheme 91) [184]. Roush has recently applied such a method in the course of the synthesis of superstolide A [185].



Scheme 92 Copper(I) catalyzed hydroboration of enyne



Scheme 93 Rhodium catalyzed formal *trans*-hydroboration of enyne

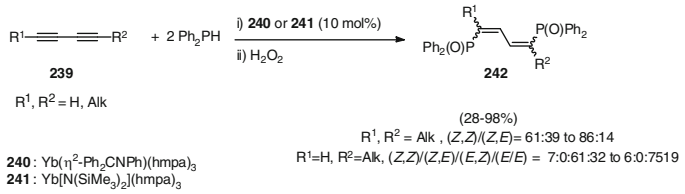
More recently, selective 3,4-hydroboration of 1,3-enynes bearing an internal alkyne moiety has been developed by Ito [186]. Copper(I) complexes catalysis allowed highly selective monoborylation of 1,3-enynes, leading to the quasi-exclusive formation of 1,3-dienylboronates **235**, with a regioselectivity depending on the substitution pattern and the ligand (Scheme 92).

In order to access the (*Z*) diastereomer, López has reported a formal *trans*-hydroboration of terminal enyne using pinacolborane in the presence of a Rh(I) complex and triethylamine [180] (Scheme 93) The yield is highly influenced by the presence of substituents on the enyne substrate.

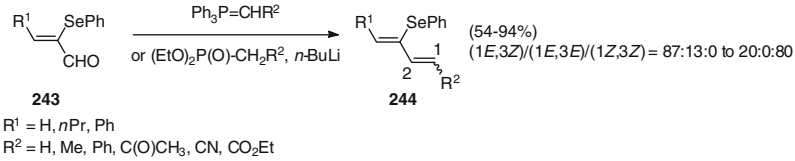
Alternatively, access to (1*Z*,3*E*)-1,3-dienes substituted by boron or tin in position 1 can be secured by hydrozirconation of 1-alkynylmetals [180].

4.5.3 Hydrophosphination

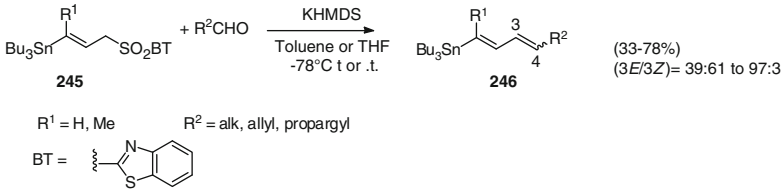
Komeyama and Takaki have described the hydrophosphination of enynes with diphenylphosphine to generate 1-phosphinyl-1,3-dienes as the sole products in excellent yields after oxidative workup. In the reported case, conjugated enynes are generated in situ by selective dimerization of terminal alkynes [187]. The same authors later developed the ytterbium catalyzed dual hydrophosphination of conjugated diynes with 2 equiv. of diphenylphosphine. The corresponding 1,4-bis (diphosphinyl)buta-1,3-dienes are then efficiently isolated after oxidative work-up. Formation of (*Z*,*Z*) diastereomers is favored with disubstituted diynes, while (*E*,*Z*) diastereomers are mainly obtained from terminal diynes (Scheme 94) [188].



Scheme 94 Ytterbium-catalyzed hydrophosphination of diynes



Scheme 95 Wittig olefination reaction



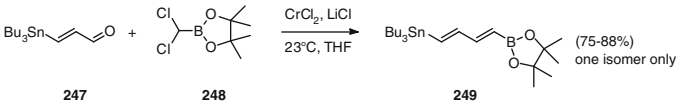
Scheme 96 Julia olefination reaction

4.6 From Vinylcarbonyl Compounds

Vinylcarbonyl compounds are common precursors for the generation of conjugated dienes. Recently, transformations including Wittig or related reactions, Julia or Takai olefination reactions, have been used to access heterosubstituted 1,3-dienes.

Selenylated 1,3-dienes have been accessed via Wittig and related reactions, starting from α-phenylselenyl α,β-unsaturated aldehydes. With non- or semi-stabilized ylides, the reaction mainly leads to the formation of the 1*Z* diastereomer. Due to steric instability, isomerization could yield the more stable 1*E* diastereomer. Expectedly, when stabilized ylides are involved in the reaction, the C1=C2 double bond configuration of the product is mainly *E* (Scheme 95) [189].

1-Tributyltin-1,3-dienes have been synthesized from tributyltin substituted benzothiazolyl sulfones and aldehydes via a Julia olefination reaction. The selectivity of the process proved higher in the presence of KHMDS as base (Scheme 96) [190].



Scheme 97 Takai olefination reaction

The Takai olefination process has been described to allow the efficient generation of hetero-bis-metallo buta-1,3-diene **249** (Scheme 97) [191]. This type of diene can then be involved in sequential Stille/Suzuki–Miyaura coupling reactions.

5 Stereoselective Preparation of Halosubstituted Conjugated Dienes

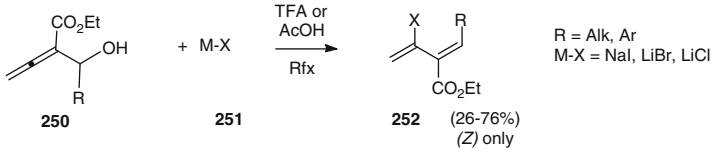
There are relatively few new methodological developments for the synthesis of halodienes. We have chosen to separate the results based on isomerization and rearrangement reactions from the previous part. This section is therefore divided into two parts.

5.1 Isomerizations and Rearrangements

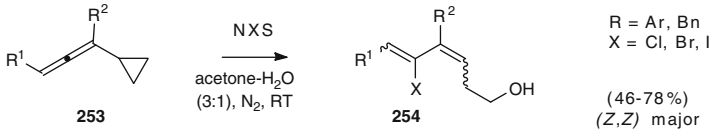
The isomerization of allenyl derivatives in the presence of halides is a potent source of halogenated dienes. It has for instance been shown some time ago that the Pd(II)-catalyzed addition of LiBr on an α-allenic acetate allows the convenient introduction of a bromine atom in the 2-position of the resulting diene [192]. Since then, it has been established that the conjugate addition of an halide on a 3-(methoxycarbonyl)-1,2-allen-4-ol **250** occurs, in acidic conditions, through an S_N2' mechanism, triggering the elimination of an hydroxyl anion (Scheme 98) [91]. Thus, a series of halo-enoates **252** could be accessed in moderate to good yields and complete *Z*-selectivity. Other conditions using $(COCl)_2$ and DMSO transform the same substrate into the corresponding chloride [193]. Note that the **250** → **252** transformation can also be catalyzed by InX_3 [194].

The cyclopropyl ring is another popular motive for the construction of halogenated dienes. Under the influence of haloniums, 1-cyclopropylallenes **253** undergo a halohydroxylation and provide 2-haloolefine **254** in medium to good yields (Scheme 99) [195]. The stereoselectivity, which tends to be mainly or exclusively *ZZ*, is significantly affected by the nature of the substituents.

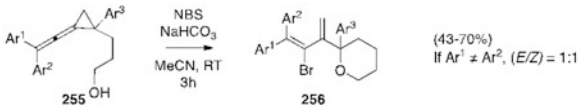
Reacting NBS or NIS with vinylidenecyclopropanes triggers a similar cationic ring-opening (NCS does not work here). When the substrate bears a remote hydroxyl group, an intramolecular addition of the alcohol on the intermediate carbocation takes place, to give access to halogenated tetrahydropyran derivatives



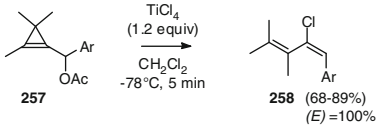
Scheme 98 Addition–elimination of MX on 3-(methoxycarbonyl)-1,2-allen-4-ol



Scheme 99 Halohydroxylation of 1-cyclopropylallenes (NXS = *N*-halosuccinimide)



Scheme 100 Access to halogenated tetrahydropyrans by ring-opening (NBS = *N*-bromosuccinimide)



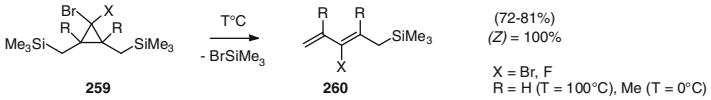
Scheme 101 Ring opening of cyclopropenylmethyl acetates under the action of $TiCl_4$

(Scheme 100) [196]. Unfortunately, when the terminal aryl substituents differ from each other, the stereoselectivity is null.

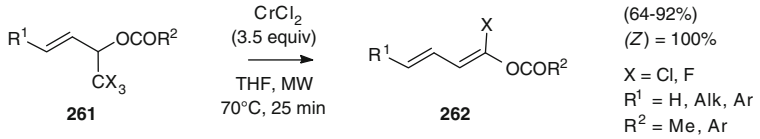
Titanium tetrachloride can also be used to promote the ring opening of cyclopropenylmethyl acetates, transforming them into (*E*)-2-halodienes (Scheme 101) [197]. This chemically efficient reaction seems to be restricted to poorly substituted substrates. The mechanism of this transformation has been studied in great detail by DFT calculations.

Let us finally mention the rearrangement of gem-dibromo- and gem-bromofluoro-cyclopropanes **259** into 2-bromo or 2-fluoro-dienes **260**, respectively (Scheme 102) [198]. Depending on the substitution of the other carbons of the cyclopropane ring, a thermal activation is needed or not.

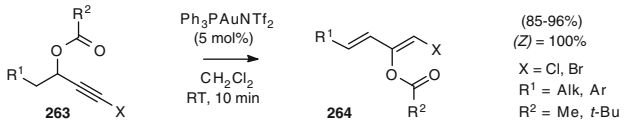
The rearrangement of metal carbenes can also provide halodienes in a very elegant manner. For instance, Fischer chromium chloro carbenes, generated from $CrCl_2$ and a trihalomethyl group borne by the substrate, were shown to evolve under microwave irradiation to provide stereoselectively (*Z*,*E*)-1-halo-1,3-dienol esters in



Scheme 102 Spontaneous rearrangements of gem-dibromo- and gem-bromofluoro-cyclopropanes



Scheme 103 Stereoselective synthesis of (*Z*,*E*)-1-halo-1,3-dienol esters catalyzed by Cr(II)



Scheme 104 Gold-catalyzed 1,2-acyloxy migration in propargylic carboxylates

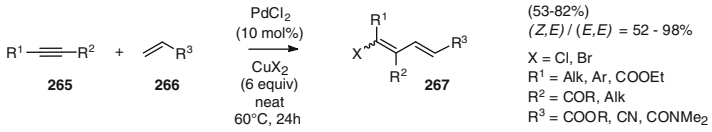
good to excellent yields (Scheme 103) [199]. The mechanism is proposed to start with the insertion of Cr in one of the C–X bonds, formation of a homo-allylic Fischer chloro carbene, and a final electrocyclic rearrangement.

Gold-catalyzed rearrangements also open new routes to halogenated dienes. Thus, advantage has been taken of a chlorine or bromine substituent to activate an alkyne and promote a gold(I)-catalyzed 1,2-acyloxy migration in propargylic carboxylates [200]. This remarkably mild method affords 1-bromo-2-acyloxy-1,3-dienes in very high yields and as a single stereoisomer (Scheme 104).

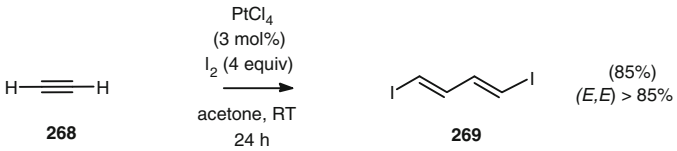
5.2 Miscellaneous Reactions

Coupling strategies have also been applied to the synthesis of halodienes. A Pd(II)-catalyzed ene–yne coupling has for instance been described recently [80]. It relies on the initial *anti*-chloropalladation of the alkyne **265**, known to occur in the presence of an excess of halide, to provide an (*E*)-vinylpalladium intermediate that undergoes a classical Heck-coupling with the activated olefin **266** in the medium. Following this mechanism, a large set of terminal chlorodienoates **267** could be prepared in good yields and generally excellent selectivities (Scheme 105).

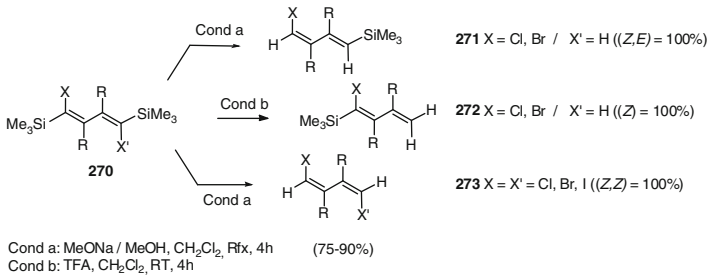
A Pt(IV)-catalyzed dimerization of acetylene **268** (yne–yne coupling) in the presence of iodine, known for a while [201], has been recently optimized. The new method leads, in good yields and selectivities, to (*E*,*E*)-1,4-diiodobuta-1,3-diene



Scheme 105 Pd(II)-catalyzed ene–yne coupling to access terminal chlorodienoates



Scheme 106 Pt(IV)-catalyzed dimerisation of acetylene in the presence of iodine



Scheme 107 Chemoselective desilylation of 1-halo-1,4-disilylated-1,3-dienes

269 (Scheme 106) [202]. This remarkable, but fragile, diene is itself an excellent building block in cross-coupling reactions [203].

The phosphorus-ylides based olefination reactions also find applications to halogenated dienes. For instance, the Horner–Wadsworth–Emmons methodology was successfully applied to (*Z*)-2-methyl-3-iodo-propenal and led efficiently to the expected γ-pyrone-substituted (*E*,*Z*)-1,3-diene (*E*/*Z* > 6:1), a key-synthon for a total synthesis of (±)-9,10-deoxytridachione [204].

The classical Wittig reaction can equally be employed to transform enals into fluorinated dienes, for instance. Thus, reacting an α-fluoro enal and an α-fluoro phosphonium ylide, difluoro-2,4-dienoates were easily obtained in fine yields and generally good selectivities [205].

Let us conclude this section with a desilylation process that transforms 1-halo-1,4-disilylated-1,3-dienes **270** into 1-halo-4-silylated or 1-halo-1-silylated-1,3-dienes, **271** and **272**, respectively, at will through a reagent-controlled process which allows the selective cleavage of one or the other silyl group (Scheme 107) [206]. The starting material **270** is readily prepared by a zirconocene-mediated coupling of silylated alkynes followed by halogenation [207]. When applied to 1,4-dihalo-1,4-bis(trimethylsilyl)-1,3-dienes, this method affords stereoselectively 1,4-dihalo-1,3-dienes **273** in good to excellent yields.

6 Conclusion

Although the methodologies employed for the stereoselective preparation of 1,3-dienes are highly dependent on the nature of the appendages, general trends can be distinguished. Whereas the vast majority of the strategies rely on transition metals catalysis to control the stereoselectivity, only a few have been designed without transition metals. Another interesting challenge is probably the directed isomerization of diene systems, which would result in stereodefined 1,3-dienes being obtained from a mixture of isomers. Developments in these two fields will probably flourish in the near future.

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Top Curr Chem (2012) 327: 147–162
DOI: 10.1007/128_2012_319

Published online: 17 April 2012

Selective Olefination of Carbonyl Compounds via Metal-Catalyzed Carbene Transfer from Diazo Reagents

Yang Hu and X. Peter Zhang

Abstract A number of transition metal complexes are capable of catalyzing selective olefination of carbonyl compounds, including aldehydes, activated and unactivated ketones, with diazo reagents in the presence of triphenylphosphine or related tertiary phosphines. These catalytic olefination reactions can be carried out in a one-pot fashion under neutral conditions with the use of different diazo reagents as carbene sources, typically affording olefins in high yields and high stereoselectivity.

Keywords Carbene · Olefination · Tertiary phosphine · Transition metal catalysis

Contents

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1 Introduction

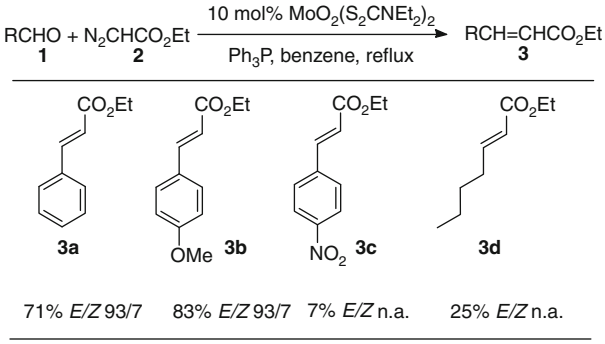
Carbon–carbon double bonds are prevalent in many natural products and serve as important functionality for a variety of organic transformations. Although new methodologies including olefin metathesis [1] have emerged, the classic Wittig reaction and its variations remain the most general approaches to the stereoselective preparation of these versatile functional groups [2–4]. Recently there has been an upsurge in the reports on catalytic olefination of carbonyl compounds by transition metal complexes with diazo reagents in the presence of triphenylphosphine (Ph_3P), enabling the Wittig reaction to be performed under neutral condition in a one-pot fashion.

The use of diazo compounds as the coupling partner of carbonyl compounds in olefin synthesis can be traced to the earliest work of Wittig [5] involving copper-catalyzed coupling of benzophenone and diazomethane in the presence of Ph_3P. In this reaction, 1,1-diphenylethylene was obtained in only 23% yield. The importance of this transformation was not recognized until the advent of transition metal complexes based on Mo [6] and Re [7]. It was shown that the use of Mo and Re complexes could deliver a much better yield in this non-basic version of the Wittig olefination reaction. The mechanisms for both $MoO(S_2CNEt_2)_2$-mediated process and methyltrioxorhenium (MTO) catalyzed system, however, are still debated and have yet to be settled [8–12]. In 2001, Woo and coworkers [12] demonstrated in a seminal report that iron(II) porphyrin complexes could efficiently catalyze olefination of aldehydes with ethyl diazoacetate (EDA) in the presence of Ph_3P. A carbene transfer mechanism was proposed for this process and is now generally accepted [13–15].

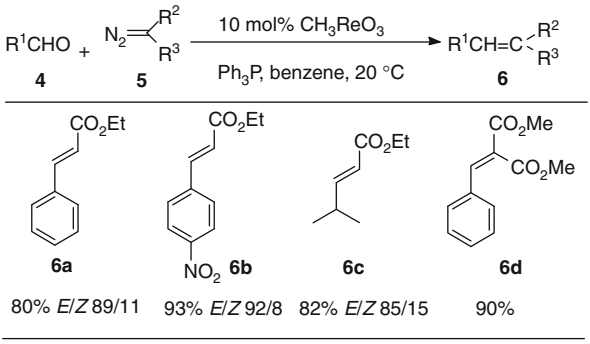
A couple of excellent reviews [13, 14] on this topic have been published, both of which covered the literature published up to 2003. Since then, new modifications, reagents, and catalysts have continued to be developed in this area, making expanded applications possible. This chapter serves to highlight the past efforts in developing this catalytic version of Wittig olefination.

2 Molybdenum Catalysis

In their search for a practical organometallic variant of the Wittig reaction, Schwartz and coworkers [16] reported that stoichiometric amounts of $MoO(S_2CNEt_2)_2$ could react with diazo reagents to form metalloazenes, which were susceptible to nucleophilic attack by phosphorane to generate olefin products. Inspired by this work, Lu and coworkers demonstrated [6] that $MoO_2(S_2CNEt_2)_2$ could catalyze olefination of aldehydes with EDA in the presence of Ph_3P. The olefin yields varied from 7% to 83% for a series of aldehyde substrates tested, with generally high *E*-selectivity observed (Scheme 1). The *para*-substituents of aryl aldehydes exhibit a drastic effect on the reactivity, with strong electron-withdrawing groups giving low yields and electron-donating groups giving high yields. This reactivity order is the opposite of that shown in common Wittig reactions.



Scheme 1 Mo-based catalytic olefination of aldehydes



Scheme 2 MTO-catalyzed olefination of aldehydes

3 Rhenium Catalysis

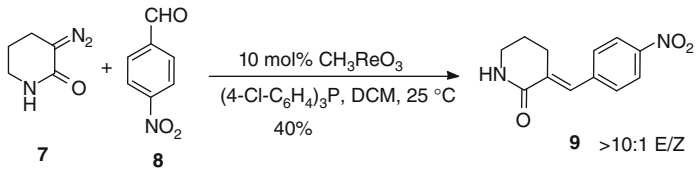
Hermann and coworkers [7] reported that MTO was capable of olefination of aldehydes using diazo reagents in the presence of Ph_3P (Scheme 2). In contrast to the Mo-based catalytic system, the Re-catalyzed olefination performed well with aryl aldehydes containing strong electron-withdrawing groups. Moreover, olefin **6d** derived from diazomalonate was obtained in 90% yield using MTO as a catalyst whereas no olefin was formed with $MoO_2(S_2CNEt_2)_2$ as a catalyst. Instead, the Mo-based system gave a stable phosphorus ylide $Ph_3P{=}C(CO_2Me)_2$, which could not even react with benzaldehyde in boiling benzene.

A direct follow-up of this work was presented by Carreira and coworkers [17] using another oxorhenium complex $ReOCl_3(PPh_3)_2$ as the catalyst. Catalyst loading as low as 1 mol% was employed without affecting the efficiency of the process. Moreover, replacement of Ph_3P by triethoxyphosphine facilitated product purification since the by-product $(EtO)_3P{=}O$ could easily be removed by aqueous work-up due to its high solubility in water. In comparison to the original MTO system

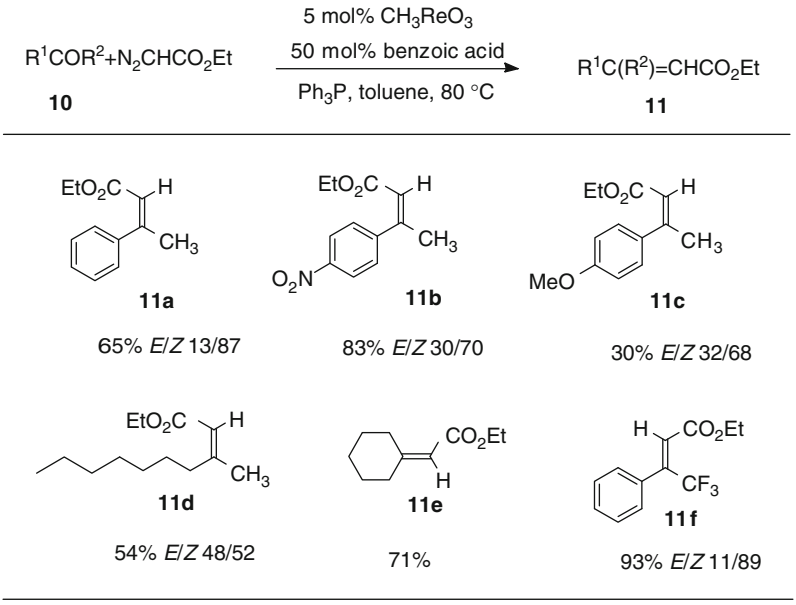
developed by Hermann, higher *E*-selectivity was generally observed for the olefination of a series of aldehydes under this modified protocol.

When the MTO/Ph_3P-based catalytic system was applied to the new diazo **7** and aldehyde **8** (Scheme 3) by Mete and coworkers [18], a poor result (<40% yield; *E*/*Z*: ~3:1) was obtained. Other tertiary phosphines bearing different electronic and steric properties were screened, including P(4-Cl-$C_6H_4)_3$, P(4-Me-$C_6H_4)_3$, P(2,4,6-MeO-$C_6H_2)_3$, PBn_3, PBu_3, P(2-furyl)$_3$, and P(2-Py)$(Ph)_2$. It was shown that phosphines with high steric hindrance or strong nucleophilicity failed to give any olefin product at all. The less nucleophilic phosphine P(4-Cl-$C_6H_4)_3$, however, was able to produce olefin **9** in 40% yield and >10:1 *E*/*Z* selectivity (Scheme 3).

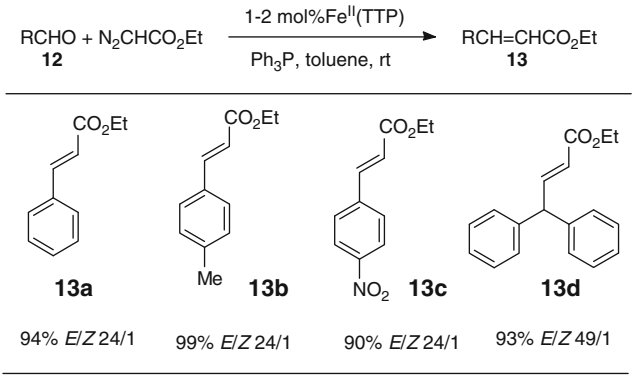
Kühn and coworkers [19] extended the MTO catalytic system to ketone substrates. Benzoic acid additive was needed to activate the ketones, a strategy that was first developed by Zhang and coworkers [20] in their investigation of olefination of unactivated ketones using an iron-based catalyst. In contrast to the *E*-selectivity observed for the iron-based system, MTO-catalyzed olefination of ketones favored *Z*-olefin products (Scheme 4). Up to 89/11 *Z*/*E* selectivity



Scheme 3 MTO-catalyzed olefination of aldehyde **8** using diazo **7**



Scheme 4 MTO-catalyzed olefination of ketones



Scheme 5 Olefination of aldehydes catalyzed by Fe(II)(TTP)

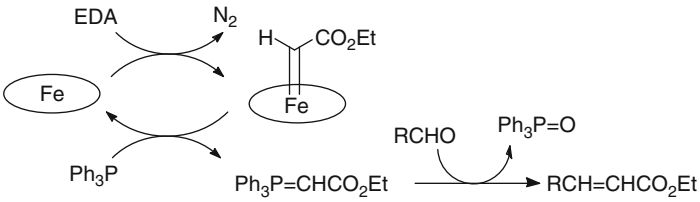
was achieved with α,α,α-trifluoroacetophenone **10f**. A conclusion was drawn that electron-deficient ketones perform better in terms of reactivity and *Z*-selectivity.

4 Iron Catalysis

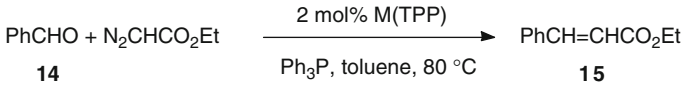
As a novel extension of the catalytic activities of metalloporphyrins, iron(II) *meso*-tetra(*p*-tolyl)porphyrin (TTP) catalyst was first reported by Woo and coworkers [12, 21] for the olefination of aldehydes with EDA in the presence of Ph_3P. Both aromatic and aliphatic aldehydes were found to be suitable substrates, generating the corresponding olefins in high yields and excellent *E*-selectivity (Scheme 5). The proposed mechanism for this reaction involves the activation of EDA with Fe(TTP) to form an iron-carbene complex, followed by carbene transfer from the iron center to Ph_3P to generate phosphorane ($Ph_3P{=}CHCO_2Et$), which in turn reacts with aldehydes to provide olefins (Scheme 6). The viability of the proposed mechanism was evidenced by two key observations. First, the phosphorane could be generated from the reaction of EDA and Ph_3P under the catalysis of 1 mol% Fe(TTP) in the absence of aldehydes. Second, the stoichiometric reaction of $Ph_3P{=}CHCO_2Et$ with benzaldehyde generated ethyl cinnamate in comparable yield and selectivity.

A catalytic cycle proposed for the analogous MTO-catalyzed reaction was believed to be unlikely for this type of olefination process because no evidence could be collected, in spite of experimental trials [12], for the existence of oxoiron (IV) species, a key intermediate for the proposed MTO cycle [7]. The other plausible mechanism proposed by Lu [6] for the Mo-based system was considered unlikely because the reactivity profile of the Fe(TTP)-catalyzed olefination reaction differs significantly from that of the $MoO(S_2CNEt_2)_2$-mediated process.

In their effort to develop practical catalytic systems for carbon–carbon bond formations, Zhang and coworkers [22] evaluated a series of commercially available metal complexes of *meso*-tetraphenylporphyrin (TPP), including V(TPP)(O),



Scheme 6 Proposed mechanism for Fe(TTP)-catalyzed olefination of aldehydes



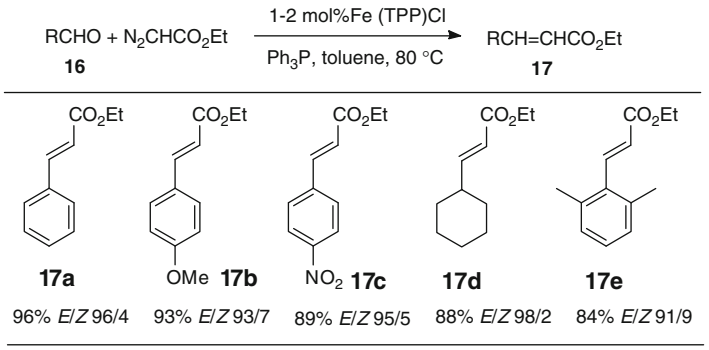
Catalyst	yield(%)	*E*/*Z*
Fe(TPP)Cl	96	96/4
Ru(TPP)(CO)	97	96/4
Co(TPP)	62	93/7

Scheme 7 Olefination of benzaldehyde catalyzed by various metalloporphyrins

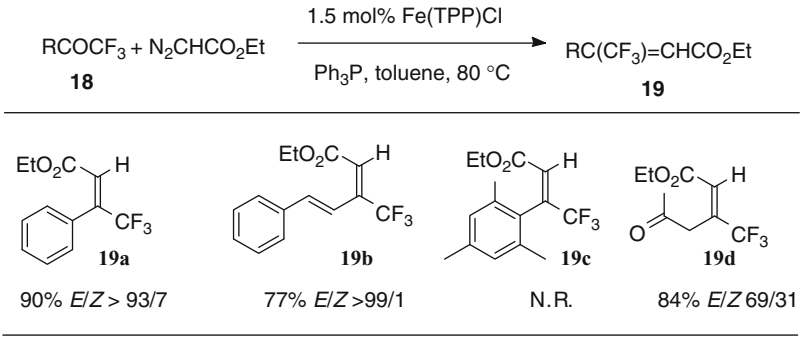
Cr(TPP)Cl, Mn(TPP)Cl, Fe(TPP)Cl, Co(TPP), Ni(TPP), Cu(TPP), Zn(TPP), and Ru(TPP)(CO), for catalytic olefination of benzaldehyde. Among the metalloporphyrins investigated, Fe(TPP)Cl emerged as the best catalyst for the reaction with both high reactivity (96% yield) and excellent selectivity (*E*/*Z*: 96/4) (Scheme 7). In addition to its low cost, the Fe(III)-based catalyst enjoys a high stability in comparison with the air and moisture sensitive Fe(II)(TPP). Although it is more expensive, Ru(TPP)(CO) gave comparable results to Fe(TPP)Cl. Co(TPP) exhibited moderate activity with isolation of ethyl cinnamate in 62% yield. Other metalloporphyrins gave no desired olefins but azines, a common side product formed by condensation of aldehyde and diazo reagents.

Compared to Mo- and MTO-based catalytic systems, Fe(TPP)Cl offered a much broader substrate scope (Scheme 8). Electron-withdrawing, electron-donating, sterically demanding, and aliphatic aldehydes all performed generally well, providing the corresponding olefins in high yields (81–99%) and excellent *E*-selectivity (*E*/*Z*: 91/9–98/2). The mechanism for Fe(TPP)Cl-mediated olefination was believed to proceed in the same catalytic cycle proposed by Woo and coworkers for the Fe(II) porphyrin complex system, because EDA is known [23] to be effective at reducing Fe(TPP)Cl in situ.

Although rhodium-based catalysts have been reported [24] for methylenation of ketones using trimethylsilyldiazomethane ($TMSCHN_2$) in the presence of Ph_3P, *stereoselective* olefination of ketones utilizing diazo reagents has met with little success [21]. Zhang and coworkers [25] extended their Fe(TPP)Cl catalytic system



Scheme 8 Olefination of aldehydes catalyzed by Fe(TPP)Cl

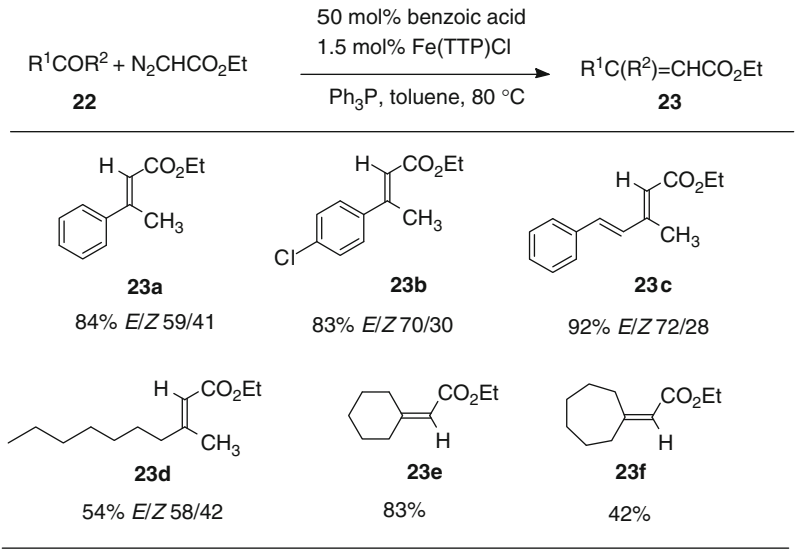


Scheme 9 Olefination of trifluoromethylketones with EDA catalyzed by Fe(TPP)Cl

to stereoselective olefination of trifluoromethyl ketones **18**, leading to efficient synthesis of β-trifluoromethyl-α,β-unsaturated esters **19** (Scheme 9), which may find potential applications in organic, material, medicinal and agricultural chemistry. Excellent *E*-selectivity (>99:1) was recorded with α,β-unsaturated trifluoromethyl ketone (**18b**). With sterically demanding substrate **18c**, however, no olefin product was observed. When substrate **18d** that contains two ketone carbonyls was used, high regioselectivity was achieved as only product **19d** was formed without observing the product from the reaction of the unactivated ketone carbonyl.

In addition to EDA, a more bulky diazo reagent, *tert*-butyl diazoacetate (*t*-BDA), was found to be suitable for the catalytic system, generating the corresponding *tert*-butyl α,β-unsaturated esters **21** with comparable yields (73–94%) and *E*-selectivity (*E*/*Z*: 62/38–99/1) (1):

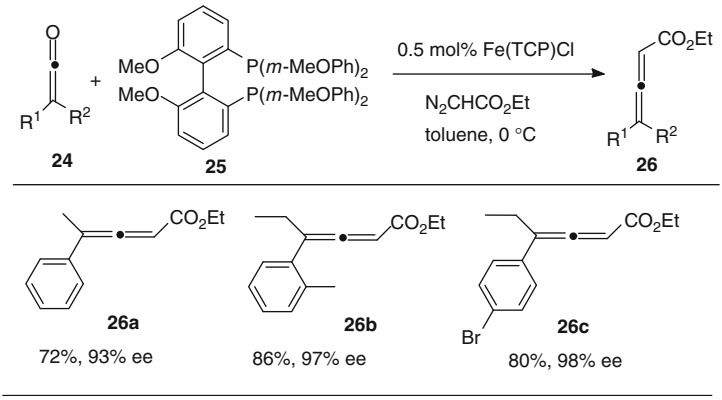
$$\underset{\mathbf{20}}{\mathrm{RCOCF_3}} + \mathrm{N_2CHCO_2{}^{\mathit{t}}Bu} \xrightarrow[\mathrm{Ph_3P,\ toluene,\ 80^{\circ}C}]{\text{1.5 mol\% Fe(TPP)Cl}} \underset{\mathbf{21}}{\mathrm{RC(CF_3)=CHCO_2{}^{\mathit{t}}Bu}} \qquad (1)$$



Scheme 10 Acid-promoted olefination of ketones with EDA catalyzed by Fe(TPP)Cl

Normal ketones, such as acetophenone or cyclohexanone, are known [21] to be inactive to the iron-porphyrin catalytic system. By comparing the reactivity of acetophenone and trifluoroacetophenone, two substrates with similar steric hindrance, as well as other experimental results, Zhang and coworkers [20] realized it is the electronic effect that is responsible for the poor reactivity of simple ketones. To circumvent this challenging problem, the operational strategy was based on the expectation that Lewis acid or hydrogen bonding would activate the simple ketones toward Fe(TPP)Cl-catalyzed olefination reaction. After the screening of different Lewis acids and Brønsted acids, benzoic acid was revealed to be the most effective additive to promote olefination of unactivated ketones with EDA in the presence of PPh_3 under catalysis of Fe(TPP)Cl (Scheme 10). Aromatic and α,β-conjugated ketones provided corresponding olefins in generally high yields, albeit in moderate *E*-selectivity. While reactions of cyclohexanones were recorded with high yields, aliphatic and other cyclic ketones were also found to be suitable substrates albeit with decreased yields. Replacement of EDA with more bulky *t*-BDA resulted in diminished yields whereas *E*-selectivity remained moderate.

Tang, Zhou and coworkers [26] further extended the Fe(III)-based catalytic olefination to ketene substrates **24** and showed that the corresponding allenic esters could be obtained in high yields using 0.5 mol% of tetra(*p*-chlorophenyl)porphyrin iron chloride (Fe(TCP)Cl) as the catalyst. When chiral phosphine **25** was used instead of Ph_3P, optically-pure allenes **26** were isolated in good yields and high enantioselectivity (Scheme 11). Since a stoichiometric amount of chiral phosphine was consumed in the process, a procedure was developed to regenerate **25** from its oxidized form. The recycled phosphine **25** was shown to be as effective as the original.

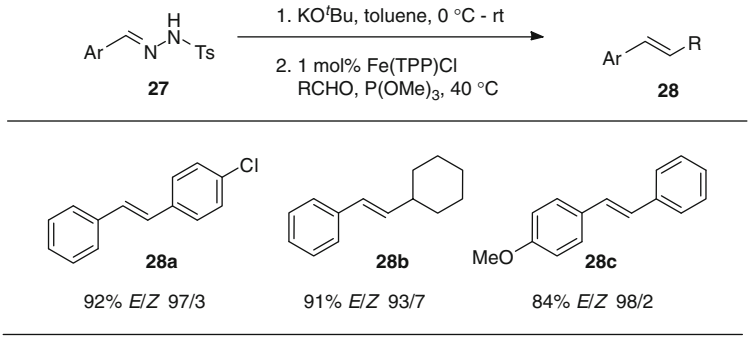


Scheme 11 Asymmetric olefination of ketenes

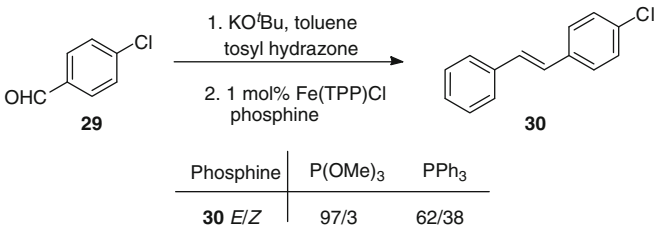
As one of the key steps involved in the Fe(TPP)Cl-catalyzed olefination, the carbene transfer from the metallocarbene to Ph_3P could proceed under neutral and mild conditions. As a result, this process proved to be amenable to other tertiary phosphines, allowing the generation of certain phosphorus ylides that have been historically elusive due to the side reactions under harsher conditions. Aggarwal and coworkers [27] discovered that, instead of using air-sensitive Fe(II) complex, Fe(TPP)Cl could be used as a precatalyst to catalyze carbene transfer from diazo reagents to $(MeO)_3P$, generating corresponding phosphorus ylides that could not be prepared by the classic method. The new class of phosphorus ylides were then allowed to react with a range of aldehydes and provided styrene derivatives **28** in high *E*-selectivity (Scheme 12).

The selectivity of the oxygen-substituted phosphorus ylides proved to be substantially different from the carbon-substituted analogs when reacted with aldehydes. For example, in the presence of $(MeO)_3P$ and catalyst Fe(TPP)Cl, phenyldiazo generated in situ could react with *p*-chlorobenzaldehyde (**29**) to produce the stilbene **30** with 97/3 *E*/*Z* selectivity (Scheme 13). When Ph_3P was applied, only 62/28 *E*/*Z* ratio of **30** was observed under the same conditions. With EDA as the diazo reagent, on the other hand, the situation was reversed and *E*-selectivity was significantly lower using $(MeO)_3P$ (*E*/*Z*: 69/31). By adding NaBr salt, however, the high *E*-selectivity was restored presumably due to an intervening Arbuzov-type reaction, which furnished the phosphonate anion that is known to give high *E*-selectivity.

To avoid the generation of stoichiometric amounts of co-product phosphine oxide ($Ph_3P{=}O$) in metal-catalyzed Wittig reactions, a protocol that requires only catalytic amounts of Ph_3P or its analogs would be highly appealing because this would make the process more environmentally friendly. In the presence of external reducing reagent sodium hydrosulfite, Tang and coworkers [28] developed a protocol of a similar kind that allowed successful olefination of aldehydes with EDA by Fe(TCP)Cl with the use of only 20 mol% Ph_3As. However, their attempt to use less



Scheme 12 Olefination of aldehydes with oxygen-substituted phosphorus ylides



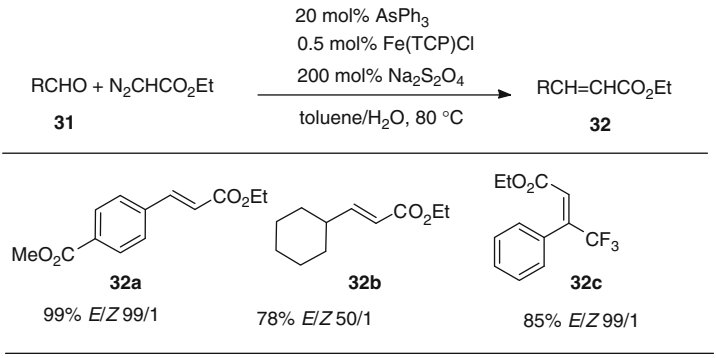
Scheme 13 Effect on *E*-selectivity by different phosphines

toxic Ph_3P was unsuccessful. Under the optimized conditions, α,*β*-conjugated esters **32** were obtained in generally high *E*-selectivity (Scheme 14).

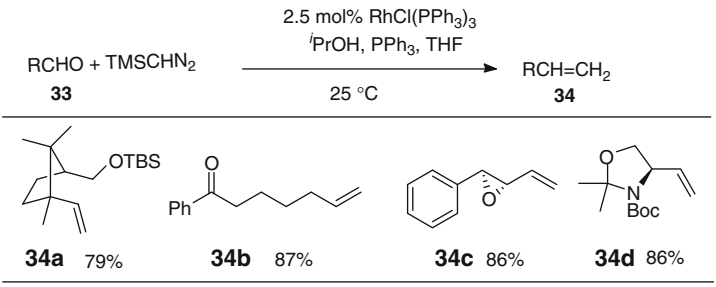
5 Rhodium Catalysis

Lebel and coworkers [29, 30] explored the methylenation of aldehydes with diazomethane (CH_2N_2) or its derivative $TMSCHN_2$ in the presence of Ph_3P using several rhodium- and ruthenium-based catalysts. The combination of $TMSCHN_2$ and isopropanol proved to be superior to CH_2N_2 in terms of reactivity and safety. Among the catalysts screened, Wilkinson's catalyst $RhCl(PPh_3)_3$ performed best. The olefination under the Rh-catalysis showed general applicability with a range of structurally disparate aldehydes (Scheme 15). Substrates containing enolizable ketone (**33b**) and racemizable protons (**33c**, **d**) were well tolerated, demonstrating the advantage of the salt-free condition enjoyed by this catalytic system over the basic conditions encountered in classic Wittig reactions.

The established rhodium-catalyzed methylenation condition was successfully applied [24] to several optically pure trifluoromethyl ketones **35** containing α-chiral centers, which are potentially racemizable under basic conditions (Scheme 16). Due to the mild and non-basic conditions employed in Rh-catalyzed olefination



Scheme 14 Olefination of aldehydes using substoichiometric amount of Ph_3As



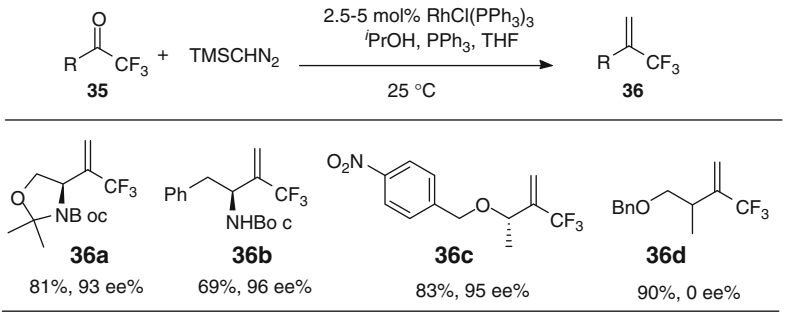
Scheme 15 Rh-catalyzed methylenation of aldehydes

reactions, trifluoromethylalkenes **36a–c** were obtained in good yields with very little racemization. As for the olefination of substrate **35d**, however, the chiral center was completely racemized during the reaction, resulting in a racemic mixture of **36d** in 90% yield.

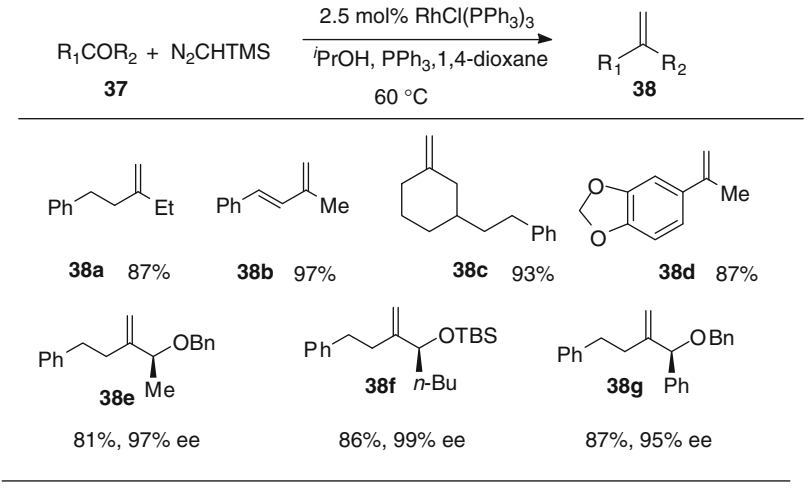
After extensive studies, rhodium-catalyzed methylenation of unactivated ketones was achieved by Lebel and coworkers [31] with the development of new reaction conditions. Use of excess isopropanol, 1,4-dioxane as solvent and higher temperatures were the key factors that led to the high yield of the corresponding olefins (Scheme 17). Substrates containing α-chiral centers were shown to proceed without racemization under the new reaction conditions (**38e–g**).

6 Ruthenium Catalysis

Ruthenium-catalyzed olefination of aldehydes with EDA in the presence of Ph_3P was first reported by Fujimura and coworkers [32] in 1998. Since then, several other Ru complexes have been reported [22, 33–35] to carry out similar reactions.



Scheme 16 Rh-catalyzed methylenation of activated ketones

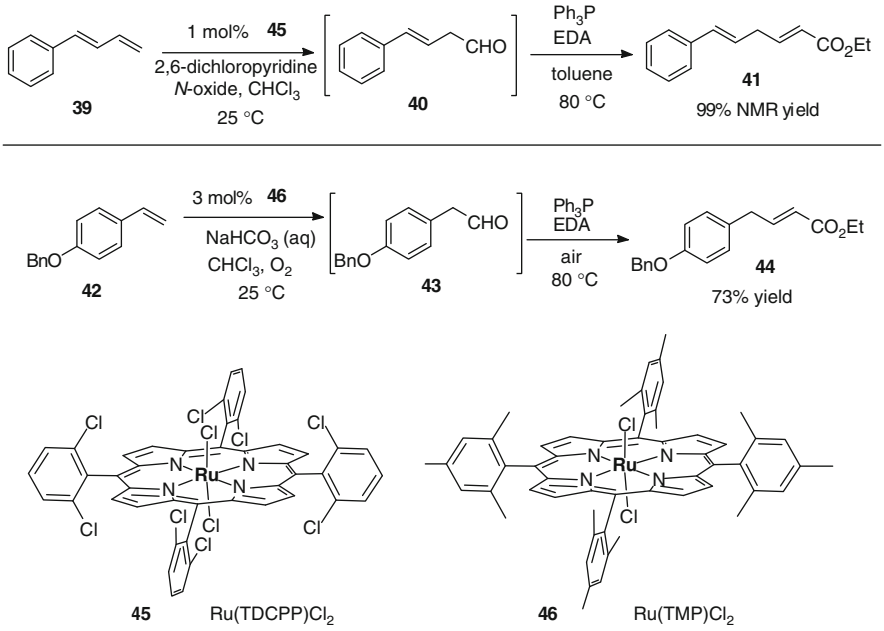


Scheme 17 Rh-catalyzed methylenation of unactivated ketones

Recently, this process was incorporated into different ruthenium-catalyzed transformations in the same reaction vessel, leading to the development of several ruthenium-promoted tandem processes.

In the investigation of Wacker-type oxidations catalyzed by Ru porphyrins, Che and coworkers [36] realized a tandem process in which Ru porphyrin **45** first catalyzed oxidation of terminal alkene **39** to aldehyde **40**, followed by a reaction in the same vessel with EDA in the presence of Ph_3P to generate the conjugated ester **41** in high yield (Scheme 18). Subsequently, they developed an aerobic protocol [37] that allowed the same tandem process to be run using only air as the oxidant.

Snapper and coworkers [38] developed a tandem process where olefination was used in conjunction with olefin metathesis. In this process, Ru complex **51** or **52** was an efficient catalyst for cross metathesis of terminal olefins **47** and **48**.

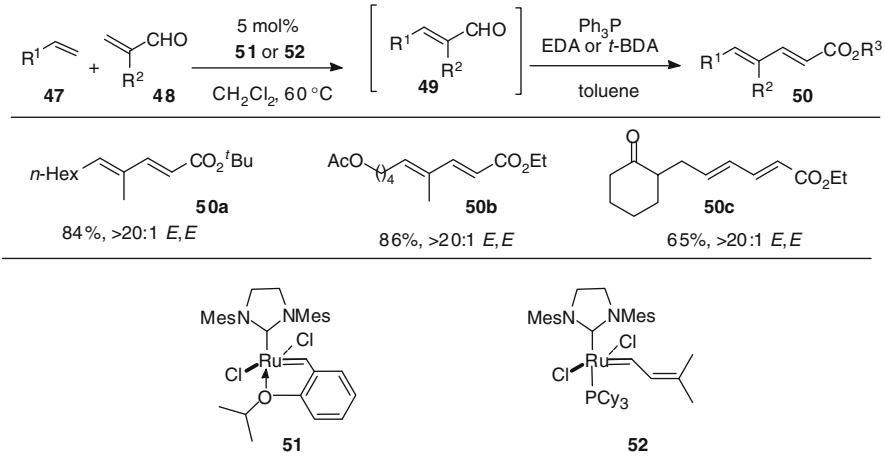


Scheme 18 Tandem Wacker-type oxidation and olefination catalyzed by Ru-porphyrin

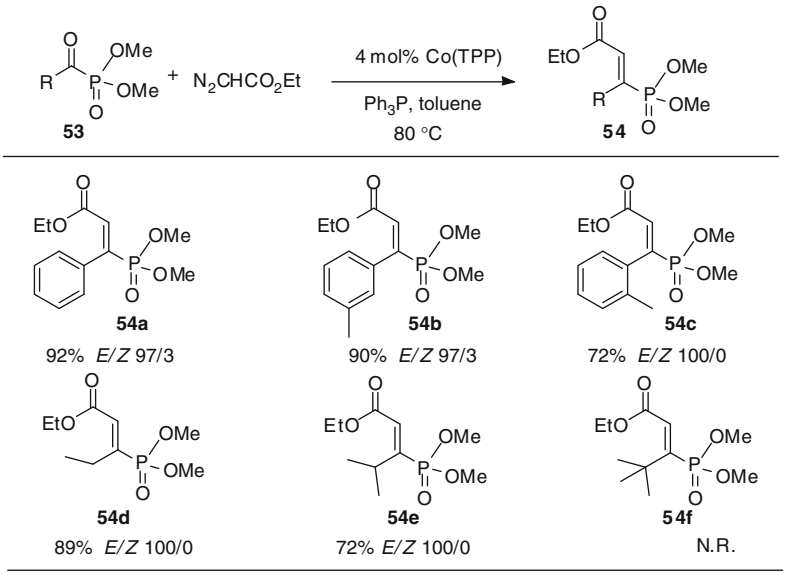
The resulting aldehydes **49** were then further reacted with EDA or *t*-BDA in the presence of Ph_3P to provide $\alpha,\beta,\gamma,\delta$-unsaturated esters **50** with >20:1 *E*,*E*-selectivity (Scheme 19).

7 Cobalt Catalysis

The first example of cobalt-catalyzed stereoselective olefination of carbonyl compounds was reported by Zhang and coworkers [22, 39], who demonstrated that EDA and Ph_3P could be coupled to form a phosphorane capable of olefination of different carbonyl compounds, including aldehydes, and activated and unactivated ketones. A follow-up work by Demir and coworkers [40] described that Co(TPP) was also an effective catalyst for olefination of acyl phosphonates **53** with EDA in the presence of Ph_3P (Scheme 20). Both aroyl and alkoyl phosphonates were found to be suitable substrates for the system and the resulting vinyl phosphonates **54** were obtained with high *E*-selectivity. Steric influence was investigated and a trend was revealed that increasing the size of the R group in **53** led to decreased reactivity but increased *E*-selectivity.



Scheme 19 One-pot syntheses of dienoic esters



Scheme 20 Olefination of acyl phosphonates catalyzed by Co(TPP)

8 Copper and Iridium Catalysis

Lebel and coworkers [41] reported that many simple copper salts and copper complexes **55**, **56** (Fig. 1) could catalyze methylenation of aldehydes and ketones using $TMSCHN_2$ and isopropanol in the presence of Ph_3P, providing the corresponding terminal olefins in moderate to good yields. While both CuCl and Cu complex **55** performed equally well for aldehyde substrates, the latter showed

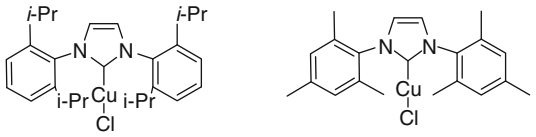
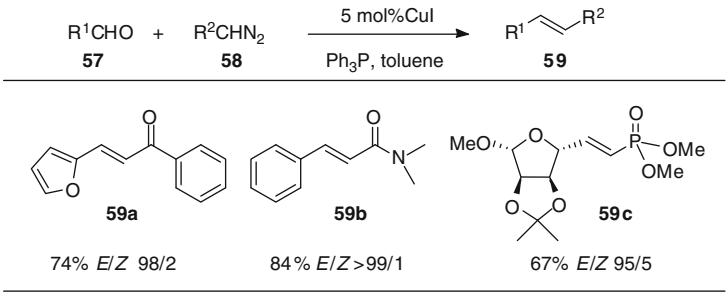


Fig. 1 *N*-Heterocycle carbene-copper complexes



Scheme 21 Olefination of aldehydes using various diazocarbonyl reagents

superiority with ketone substrates, as substantially higher yields were recorded. CuI was further utilized [42] to investigate olefination of aldehydes with other diazo reagents **58** derived from esters, ketones, amides, and phosphonates, generating the corresponding olefins in good yields and high *E*-selectivity (Scheme 21). This process was successfully applied to a short synthesis of natural product scutifoliamide A. Iridium complexes such as $[IrCl(cod)]_2$ and $IrCl(CO)(PPh_3)_2$ were also demonstrated [43] to be effective catalysts for olefination of aldehydes.

9 Conclusions

The past 2 decades have witnessed the great achievement of direct coupling of carbonyl compounds and various diazo reagents catalyzed by different transition metal complexes in the presence of Ph_3P, generating olefins in typically high yields and high *E*-selectivity. A salient feature of this process is the non-basic condition employed, which greatly broadens the substrate scope of the classic Wittig reaction. Although high *Z*-selectivity was reported in a single case with the MTO system, the challenge in this field is to develop an efficient system that can provide dominant *Z*-olefins. There is still room for improvement with reactions of ketone substrates in terms of selectivity and reactivity. Extension of this chemistry to other carbonyl substrates such as esters and amides would be another important future direction.

Acknowledgments We are grateful for financial support by the National Science Foundation (CHE-0711024).

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Top Curr Chem (2012) 327: 163–196
DOI: 10.1007/128_2012_318

Published online: 17 April 2012

Selective Alkene Metathesis in the Total Synthesis of Complex Natural Product

Xiaoguang Lei and Houhua Li

Abstract Alkene metathesis has had a significant impact on the selective and efficient formation of carbon–carbon bonds and the advances of complex natural product total synthesis over the last two decades. In this chapter we highlight a number of recent examples of total syntheses in which selective alkene metathesis plays a vital role in the design and implementation for efficient synthesis. In this regard, we expect the influence of this transformation will continue to shape the landscape of the state of the art and science of natural product total synthesis.

Keywords Alkene metathesis · Cascade reaction · Natural product · Stereoselective synthesis · Total synthesis

Contents

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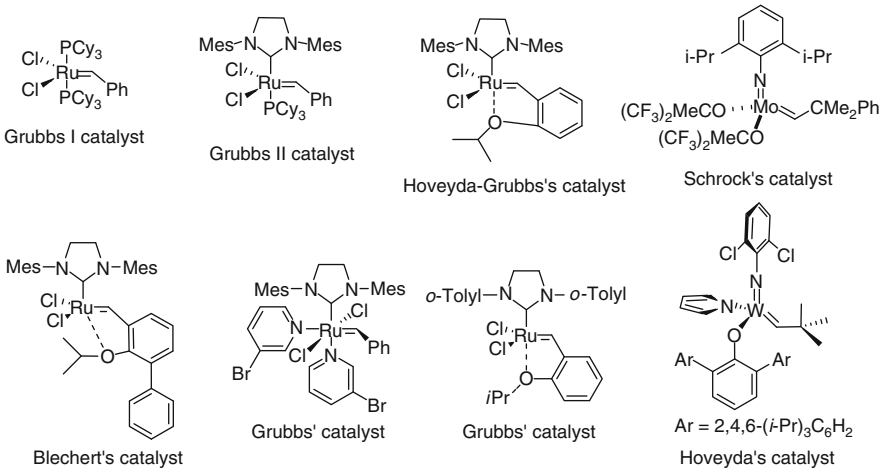
1 Introduction

Alkene metathesis ("metathesis" means "change of position" in Greek) has significantly influenced synthetic chemistry and revolutionized the synthesis of complex natural products over the last two decades [1–14]. Organic chemists in both academic and industrial laboratories have demonstrated the broad application of this transformation. The history of alkene metathesis began with the serendipitous discovery of ring opening polymerization of cycloalkenes and the disproportionation of linear alkenes in the 1960s [15–18]. The mechanism of olefin metathesis was initially proposed by Chauvin and Hérisson in 1971, which indicated that metal carbenes are catalytically active species [19]. In the mid-1970s, the first well-defined tungsten carbene catalyst for alkene metathesis was developed by Katz and coworkers [20, 21]. In the late 1980s, more practical molybdenum based catalysts were developed by Schrock et al. [22], and later were used by Grubbs and Fu in ring closing metathesis (RCM) to construct heterocycles [23, 24]. In 1992, Grubbs and coworkers disclosed the first vinylidene ruthenium catalyst and its successful application in both ring opening and closing metathesis [25]. Shortly after this discovery, in 1995, Grubbs et al. further refined the initial catalyst and developed the first air-stable and robust ruthenium based catalyst known as Grubbs first-generation catalyst (Grubbs I) [26]. The replacement of phosphine ligand by the *N*-heterocyclic carbene ligand led to the discovery of more stable and reactive Grubbs second-generation catalyst (Grubbs II) [27]. Besides Grubbs' laboratory, Schrock and Hoveyda's laboratories have also developed a number of effective catalysts for alkene metathesis [28]. To date, many effective catalysts have been devised to enable more versatile and robust applications of alkene metathesis in the synthesis of complex molecules, particularly natural products.

Alkene metathesis has significant advantages in natural product synthesis for several reasons. First, alkene moieties broadly exist in numerous natural products, and alkene metathesis allows facile access from the readily available or easily prepared olefins to those that are difficult to access. Second, alkene metathesis reactions either do not produce any by-product or only generate the volatile ethylene. Third, alkenes are relatively stable in the multistep synthesis, and are sufficiently reactive to be used in a wide range of transformations to generate other functionalities under specific reaction conditions. Finally, and most importantly, with the help of effective catalysts, alkene metathesis can provide remarkable selectivities (regio-, chemo-, and stereoselectivity) in the challenging synthetic operations.

The aim of this review is to highlight the impact of alkene metathesis on the total synthesis of complex natural products, and emphasize the selectivities that have been achieved in the application of this transformation to construct carbon–carbon double bonds. Due to the limited space, we only selected the most recent (normally in the past 5 years) examples of selective alkene metathesis as a key step for the total synthesis of natural products. We hope this review will provide a useful and inspiring source for synthetic chemists who plan to utilize alkene metathesis in their efforts to accomplish the total synthesis of complex natural products.

List of Commonly Used Catalysts in Total Synthesis



2 Selective Alkene Ring-Closing Metathesis

Alkene RCM has been proved to be one of the most reliable and powerful methods for ring formation [29]. A large number of ring systems including both medium and large sized rings can be efficiently constructed by this tool. Therefore, alkene RCM is now broadly applied in the total synthesis of complex natural products. However, the selective alkene RCM in the presence of multiple alkene moieties is considerably challenging, which requires careful design and implementation.

In 2008, Donohoe and coworkers reported the total synthesis of (−)-(Z)-deoxpukalide (**1**) [30], a complex marine natural product with an intriguing 14-membered carbon macrocyclic skeleton containing a trisubstituted furan moiety (Fig. 1). The key features in the synthesis involve a selective alkene RCM/aromatization protocol to prepare the disubstituted furan methyl ester (**3**) as well as a late stage RCM to furnish the butenolide moiety. Since the five-membered ring formation is more favored, the marked exomethylene functionality was intact under the alkene RCM conditions.

The amphidinolides are a unique family of antitumor natural products isolated from dinoflagellates of the genus *Amphidinium* [31]. Due to their complex and fascinating structures as well as promising biological activities, the amphidinolides have attracted considerable attention in the synthetic community [32]. Amphidinolide E (**5**) is one of the most complex molecules in this family. In 2006, Roush and coworkers reported a convergent and highly stereocontrolled approach to the total synthesis of amphidinolide E (**5**) (Fig. 2) [33]. The key formation of the C5–C6 olefin and closure of the 19-membered macrocycle in the presence of several alkene

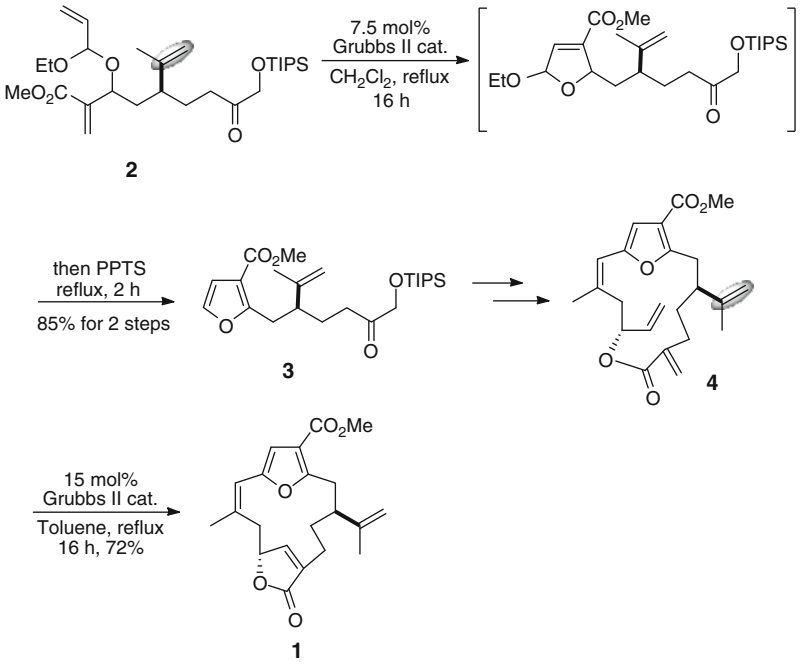


Fig. 1 Total synthesis of (−)-(Z)-deoxypukalide (**1**) by Donohoe et al.

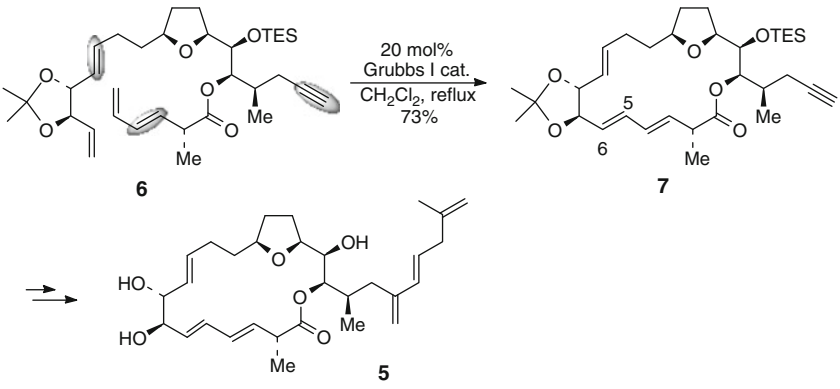


Fig. 2 Total synthesis of amphidinolide E (**5**) by Roush et al.

and alkyne moieties proved to be very challenging. This transformation could only be achieved by using Grubbs' first generation catalyst to generate the desired diene (**7**) in 73% yield. The authors also showed that use of the more active Grubbs' second generation catalyst or Grubbs–Hoveyda catalysts only resulted in decomposition of the polyene precursor (**6**).

In the total synthesis of the related natural product amphidinolide H (**8**) [34], Fürstner et al. also utilized the late stage alkene RCM strategy for the challenging

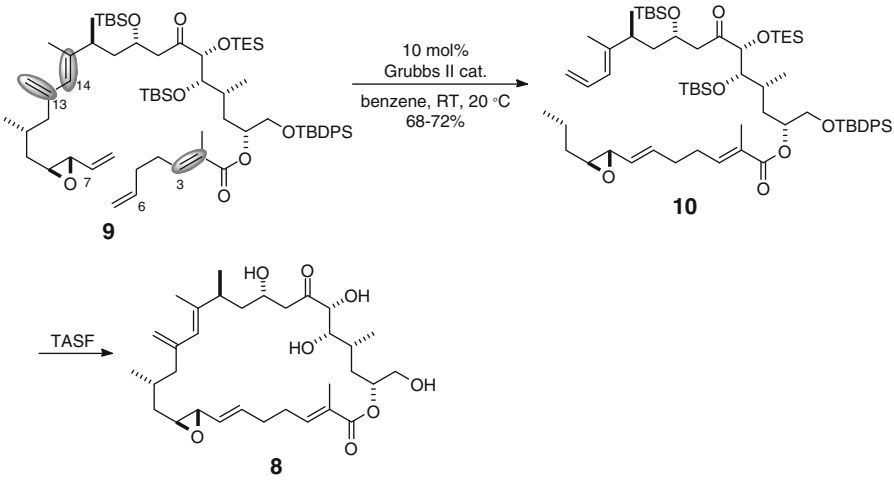


Fig. 3 Total synthesis of amphidinolide H (**8**) by Fürstner et al.

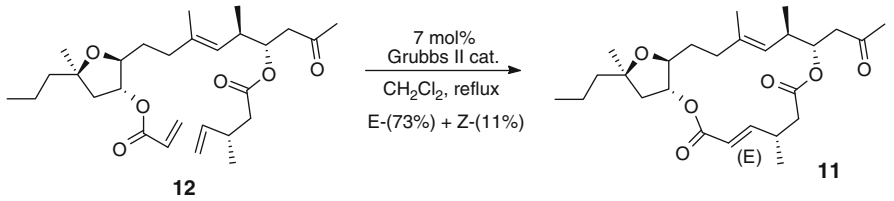


Fig. 4 Total synthesis of (−)-amphidinolide X (**11**) by Lee et al.

macrocyclization (Fig. 3). In the presence of multiple alkene moieties as well as the labile vinyl epoxide, the selective alkene RCM was realized by using Grubbs' second generation catalyst to afford the desired product (**10**) in 68–72% yield as the required *E* isomer only.

Similarly, Lee and coworkers reported the total synthesis of amphidinolide X (**11**) through the key alkene RCM using Grubbs' second generation catalyst to provide the desired natural product (**11**) in 74% yield, accompanied by the *Z* isomer byproduct in 11% yield (Fig. 4) [35].

Kendomycin (**13**) was isolated from different *Streptomyces* species, which showed potent antibacterial and cytostatic activities [36, 37]. Due to its challenging chemical structure and interesting biological profile, a number of impressive total syntheses have been accomplished [38]. However, all attempts to achieve 13,14-macrocyclization and formation of the desired 13,14-*E*-olefin by alkene RCM were unsuccessful [39–41]. In 2009, Mulzer and coworkers described a novel approach to the total synthesis of kendomycin (**13**) via the selective alkene RCM at C10–C11 as one of the key steps (Fig. 5) [42]. In this work, they demonstrated that RCM with Grubbs II catalyst smoothly facilitated ring closure to form the 10,11-*E*-olefin (**15**)

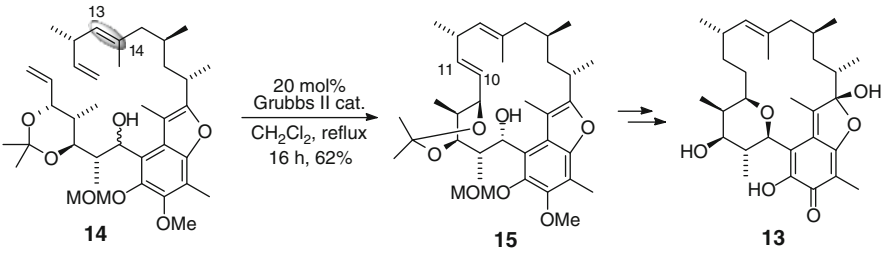


Fig. 5 Total synthesis of (−)-kendomycin (**13**) by Mulzer et al.

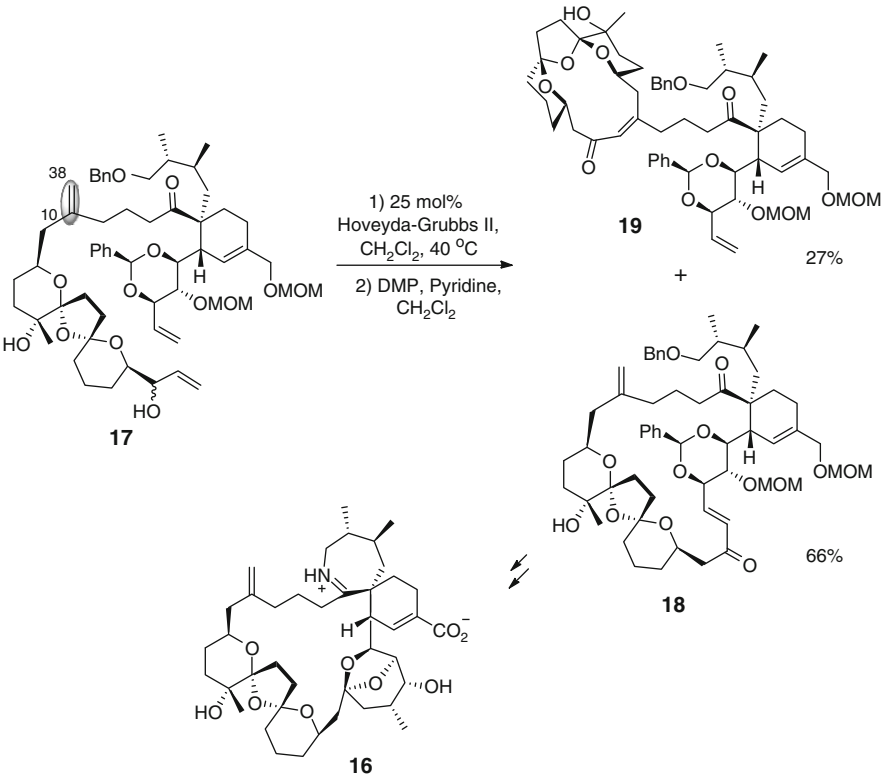


Fig. 6 Total synthesis of (+)-pinnatoxin A (**16**) by Zakarian et al.

exclusively, which highlighted the unparalleled potential of alkene RCM for coupling monosubstituted olefin residues.

Another impressive example of macrocyclization through alkene RCM was reported by Zakarian et al. in their total synthesis of complex marine natural product (+)-pinnatoxin A (**16**) (Fig. 6) [43]. In this study, the remarkable formation of the 27-membered all-carbon and highly functionalized macrocycle was

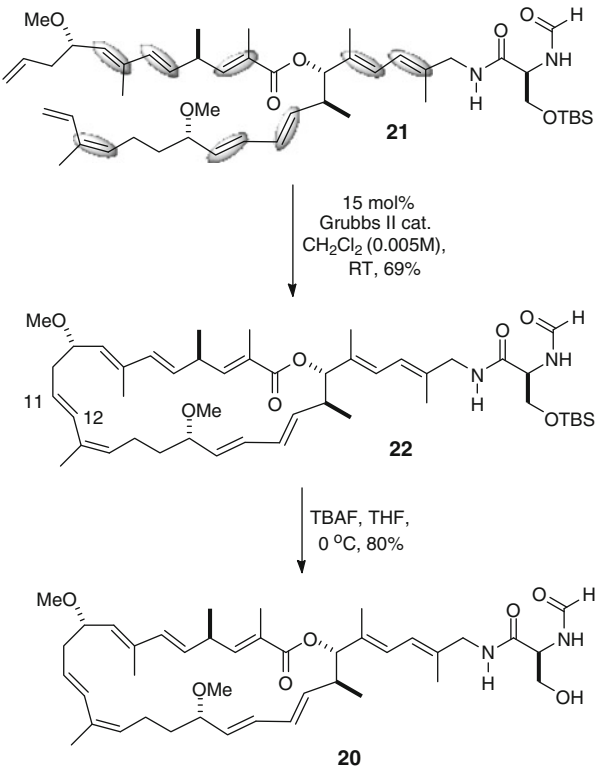


Fig. 7 Total synthesis of iejimalide B (**20**) by Fürstner et al.

efficiently achieved by alkene RCM. Under the reaction condition with Hoveyda–Grubbs II catalyst, the desired macrocycle (**18**) and the undesired isomer (**19**) were produced in 66% and 27% yields, respectively. The formation of the undesired isomer is due to the competitive cyclization involving the 1,1-disubstituted alkene at C10–C38. It was also reported that no reaction was observed when Grubbs I catalyst was employed.

One of the most remarkable recent examples using a selective alkene RCM strategy for the total synthesis of complex macrolide natural product was depicted by Fürstner and coworkers (Fig. 7) [44]. Iejimalide B (**20**) is a highly complex marine natural product isolated from tunicates harvested off the south Japanese coast [45]. This natural product showed very potent anticancer activities both in vitro and in vivo, which rendered it an intriguing synthetic target. However, the daunting chemical structure with highly fragile polyunsaturated systems for iejimalide B (**20**) requires careful design and effective execution in order to accomplish its total synthesis. The risk of using RCM for the final macrolization had been evaluated as, first, it is extremely challenging to selectively activate two out of ten double bonds in the polyene precursor, and, second, conjugated dienes are

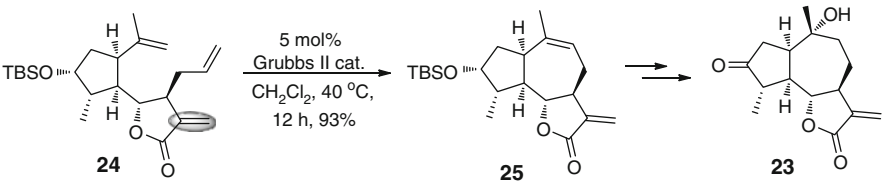


Fig. 8 Total synthesis of (+)-chinensiolide B (**23**) by Hall et al.

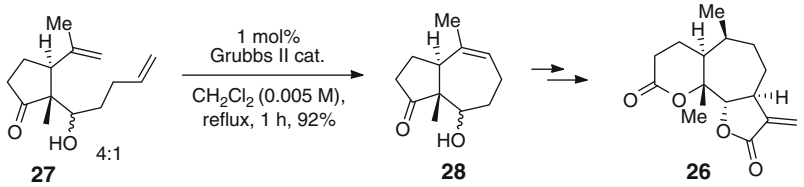


Fig. 9 Total synthesis of psilostachyin C (**26**) by Lei et al.

known to be problematic under metathesis conditions. With these analyses, the authors decided to select the C11–C12 double bond as the only promising position for the final RCM-based macrocyclization. As a result, cyclization of this polyene substrate (**21**) with the aid of Grubbs II catalyst amazingly provided the desired 24-membered macrocycle (**22**) in 69% yield as a single *E* isomer, which allowed for the accomplishment of total synthesis of iejimalide B (**20**). This particularly instructive work further highlights the strategic advantages of selective RCM for the endeavors of complex natural product synthesis.

The construction of a seven-membered ring could be achieved by alkene RCM, which has been proved to be an effective method for the synthesis of midsized ring systems [46]. However, when the final alkene is tri- or tetrasubstituted, this transformation can be problematic. In 2010, Hall et al. reported the total synthesis of (+)-chinensiolide B (**23**), a bioactive sesquiterpene lactone, which nicely demonstrated the feasibility of using selective alkene RCM for the formation of a seven-membered ring with a trisubstituted alkene moiety (Fig. 8) [47]. In this case, a chemoselective alkene RCM of the triene intermediate (**24**) using 5 mol% of Grubbs' second generation catalyst smoothly afforded the desired tricyclic product (**25**) in 93% yield. Conceivably, the steric hindrance of the α-methylene-γ-lactone motif and formation of a bridgehead olefin rendered the possible six-membered ring less favored, which allowed the α-methylene-γ-lactone moiety to be intact. Lei and coworkers reported the similar strategy to construct the seven-membered ring with a trisubstituted alkene for the total synthesis of psilostachyin C (**26**) (Fig. 9) [48].

The formation of a nine-membered ring system through alkene RCM also proved to be challenging [46]. In 2008, Hoppe et al. reported the asymmetric total synthesis of (+)-vigulariol (**29**), a cytotoxic and tetracyclic diterpene which was isolated from the sea pen *Vigularia juncea* (Fig. 10) [49]. The key step in this total synthesis involves the construction of the oxacyclononene framework by

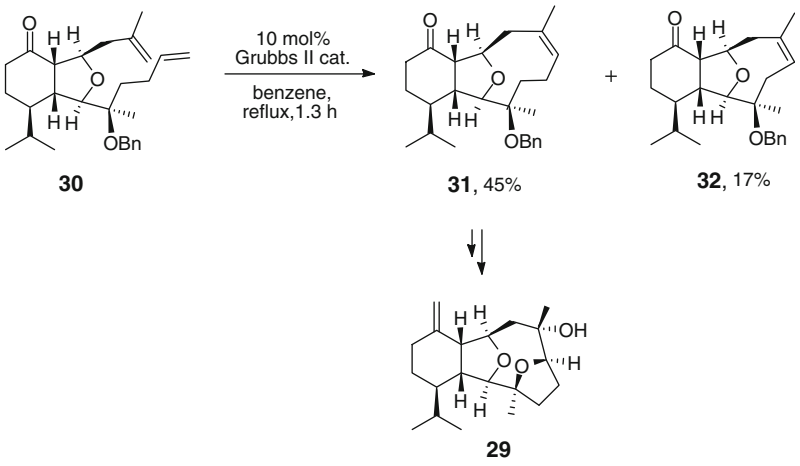


Fig. 10 Total synthesis of (+)-vigulariol (**29**) by Hoppe et al.

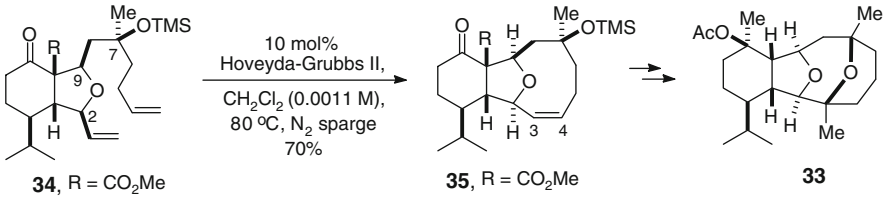
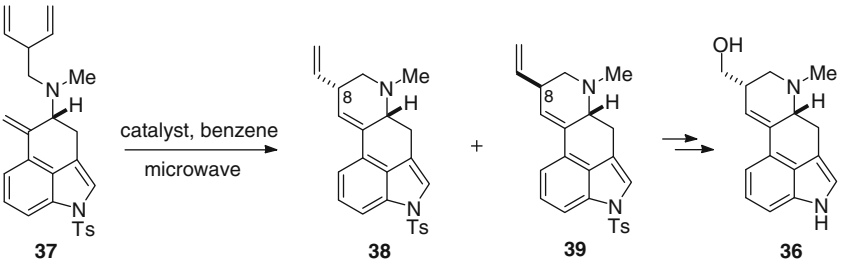


Fig. 11 Total synthesis of (+)-polyanthellin A (**33**) by Johnson et al.

selective alkene RCM, which was previously regarded to be problematic. In this study, Grubbs I and Hoveyda's catalysts did not provide any desired product. In contrast, Grubbs II catalyst yielded the desired nine-membered ring (**31**) in 45% yield, along with the eight-membered ring byproduct (**32**) in 17% yield. The loss of a methylene group during RCM is presumably due to an olefin isomerization event occurs prior to the RCM [50]. In 2009, Johnson and coworkers disclosed the total synthesis of a related natural product polyanthellin A (**33**), in which the key RCM was conducted with Hoveyda–Grubbs II catalyst to generate the desired nine-membered ether (**35**) (Fig. 11) [51].

Alkaloids are a large family of natural products that represent diverse and complex structures as well as important biological activities. Total synthesis of alkaloid has a rich history and has been evoking broad interest in the synthetic community [52]. Numerous strategies have been reported for the construction of polycyclic skeletons in alkaloid synthesis. In this regard, alkene RCM has been proved to be an effective means for the syntheses of a number of alkaloids of varying complexity [53].

One recent example was reported by Martin et al. in the first total synthesis of (+)-isolysergol (**36**) [54]. This synthesis was accomplished by a novel approach that features a late stage microwave-promoted, diastereoselective alkene RCM catalyzed by a chiral molybdenum catalyst to construct the desired ring system



Condition	Product (yield[%])		
A	**38** (36)	+	**39** (8)
B	**38** (55)	+	**39** (22)
C	trace		

A: Schrock's cat., benzene, microwave 300 W, 10 min;
B: 50 mol% (S)-Schrock-Hoveyda cat., benzene, microwave 50 W, 30 min;
C: (*R*)-Schrock-Hoveyda cat., benzene, microwave.

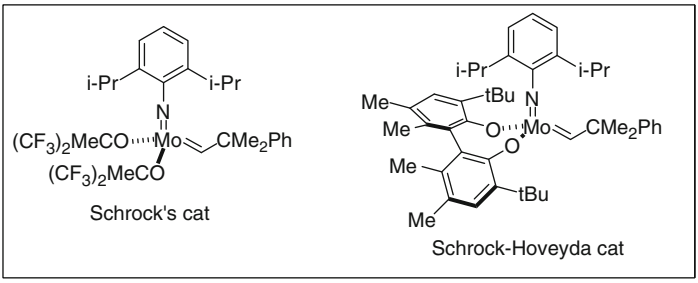


Fig. 12 Total synthesis of (+)-isolysergol (**36**) by Martin et al.

and set the correct stereocenter. The formation of C9–C10 double bond via an asymmetric RCM presented a great challenge as it required the selective interaction of catalyst with one of the two diastereotopic vinyl groups prior to the RCM with the disubstituted exomethylene. Initially, the authors observed that treatment of the triene precursor (**37**) with Grubbs I and II catalysts as well as Schrock's catalyst either at room temperature or under thermal conditions provided no cyclization products. However, microwave irradiation (300 W, 10 min) of triene in the presence of Schrock's catalyst afforded two cyclization products (**38**) and (**39**) in 36% and 8% yields, respectively. Further optimization of the reaction conditions showed that the desired product (**38**) could be formed in 55% yield using (S)-Schrock–Hoveyda catalyst under microwave condition. Interestingly, using the enantiomeric (R)-Schrock–Hoveyda catalyst only led to trace amounts of the cyclization products, which was presumably due to a mismatched consequence. This notable study demonstrated the feasibility of using chiral catalyst to achieve the diastereoselective alkene RCM (Fig. 12).

The successful application of diastereoselective alkene RCM as a key step for alkaloid synthesis was also documented by two very recent examples. 1n 2011,

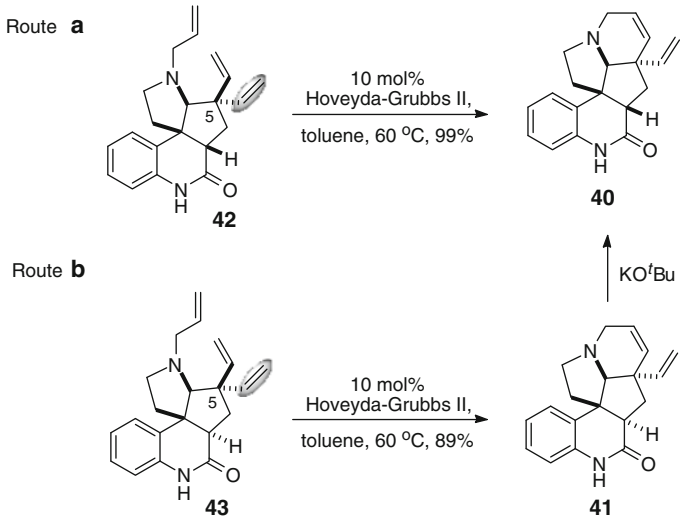


Fig. 13 Total syntheses of *Melodinus* alkaloids (±)-meloscine (**40**) and (±)-epimeloscine (**41**)

Mukai and coworkers reported the concise total synthesis of *Melodinus* alkaloid (±)-meloscine (**40**) [Route (a), Fig. 13], in which the final key transformation involved an alkene RCM of the triene precursor (**42**) in the presence of Hoveyda–Grubbs II catalyst [55]. The RCM between the *N*-allyl group and the top-oriented vinyl moiety exclusively occurred to generate the desired diastereomer (**40**) in almost quantitative yield. The extremely high diastereoselectivity could be rationalized on the basis of ring strain to favor one conformer. Shortly after this work, Curran et al. disclosed another approach to the total syntheses of (±)-epimeloscine (**41**) and (±)-meloscine (**40**) applying the same RCM protocol for the final ring formation [Route (b), Fig. 13] [56].

In terms of the application of selective alkene RCM for multiple ring formation, Martin et al. reported a very interesting example in their total synthesis of indole alkaloid (±)-pseudotabersonine (**44**) [57]. In this case, a highly functionalized tetraene substrate (**45**) underwent double RCMs in the presence of Hoveyda–Grubbs II catalyst to afford a mixture of two diastereomers (**46**) (Fig. 14). During this process the high regioselectivity for alkene RCM was achieved, which was worthy of note.

In summary, for the last decade, selective alkene RCM has become a powerful tool for the synthesis of complex natural products. This method has been broadly applied to the construction of different ring systems including both medium-size (five- to ten-membered) and large rings. For the polyene substrate, terminal and less substituted alkenes are generally more reactive. In addition, steric effects, conformational effects as well as choice of catalysts are also key factors to achieve the selectivity.

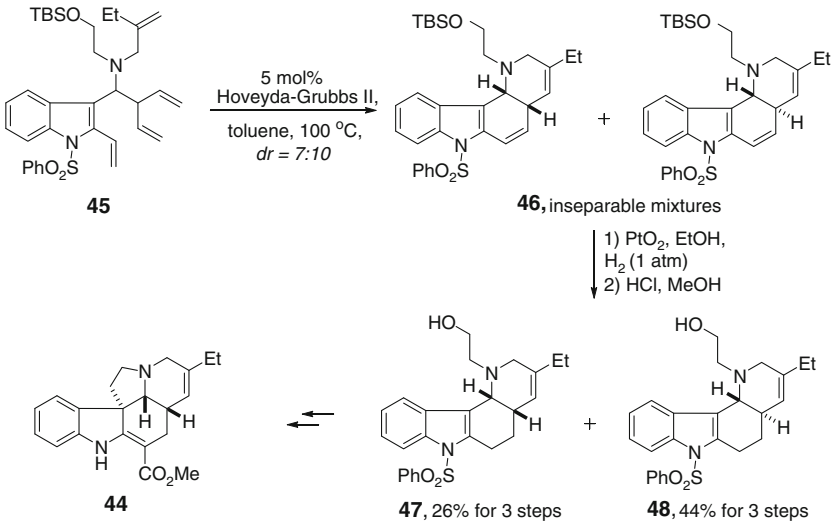


Fig. 14 Total synthesis of (±)-pseudotabersonine (**44**) by Martin et al.

3 Selective Relay Alkene Metathesis

In the previous section we have demonstrated that alkene RCM is a powerful and broadly applicable method for the synthesis of complex natural products. However, not every diene or polyene substrate can be successfully cyclized even with the significant advantages available by variation of reaction conditions including catalyst selection, additive use, solvent choice, and concentration, etc. In this regard, selective relay alkene metathesis provides synthetic chemists with an alternative for reviving these otherwise dead systems when such a limitation is encountered.

Hoye's laboratory has pioneered in the field of relay alkene metathesis. In 2004, Hoye and coworkers showed the first example of using relay ring closing metathesis (RRCM) for the synthesis of tetrasubstituted alkene (**49**) (Fig. 15) [58].

The first successful application of RRCM in complex natural product synthesis was reported by Porco et al. in 2005 (Fig. 16) [59]. In the synthesis of oximidine III (**51**) they successfully cyclized the polyene precursor (**52**) to access macrolide (**53**) with a *Z*-double bond using Hoveyda–Grubbs catalyst.

One of the most remarkable examples for the synthesis of macrolide natural product using selective relay alkene RCM as a key step was reported by Trauner et al. in 2007 (Fig. 17) [60]. Archazolid B (**54**) was originally isolated from the myxobacterium *Archangium gephyra* and showed highly potent inhibitory activity against mammalian V-ATPases. This highly unsaturated polyketide has unusual structural features including a 24-membered macrolactone ring with a rare (*Z*,*Z*,*E*)-triene moiety. Considering the normal RCM may favor the initiation at the terminal alkene instead of at the diene moiety which would presumably lead to the undesired reaction pathway to produce an unsaturated δ-lactone, the authors decided to

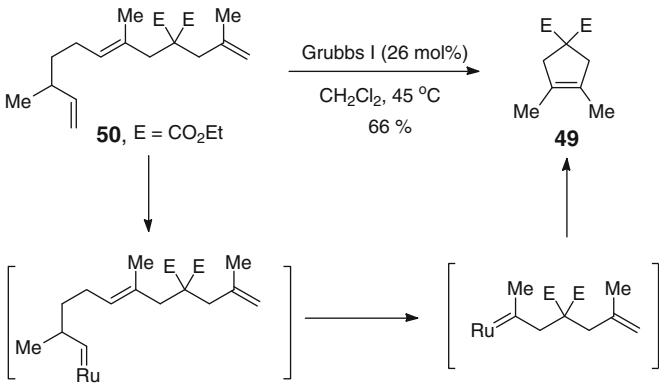


Fig. 15 Pioneering work of relay alkene metathesis by Hoye et al.

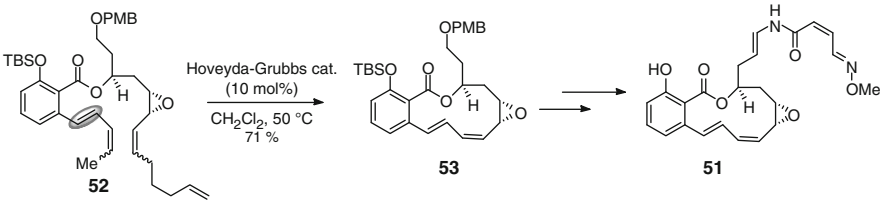


Fig. 16 Total synthesis of oximidine III (**51**) by Porco et al.

facilitate the desired initiation through selective relay RCM. However, the daunting challenge still exists in terms of selectively activating one out of nine double bonds. Gratifyingly, the selective relay alkene RCM of precursor (**55**) using Grubbs II catalyst proceeded as planned to generate the desired macrocycle (**56**) in 27% yield, which allowed for the completion of the total synthesis of (−)-archazolid B (**54**).

Relay alkene RCM also proved to be a useful tool for the construction of medium sized ring systems. In a recent example of natural product total synthesis, Hoye and coworkers have nicely demonstrated this point (Fig. 18) [61]. (+)-Peloruside A (**57**) is a highly cytotoxic marine natural product isolated from the New Zealand sponge *Mycale hentscheli* [62]. Despite total syntheses of peloruside A having been previously reported by several groups, Hoye and coworkers developed a novel strategy to access this molecule efficiently, in which the versatility of relay RCM was highlighted. The highly functionalized lactone intermediate (**59**) was smoothly prepared in 70% yield through relay RCM using Grubbs II catalyst.

Another interesting example of selective relay alkene RCM in the presence of multiple alkene and alkyne moieties was disclosed by Crimmins et al. [63]. Mucocin (**60**) was isolated from the leaves of *Rollinia mucosa* and showed potent antitumor activity [64]. Crimmins and coworkers described an enantioselective total synthesis of (−)-mucocin in 2006 (Fig. 19). In this study they highlighted a key step using selective relay alkene RCM to form the five-membered cyclic ether.

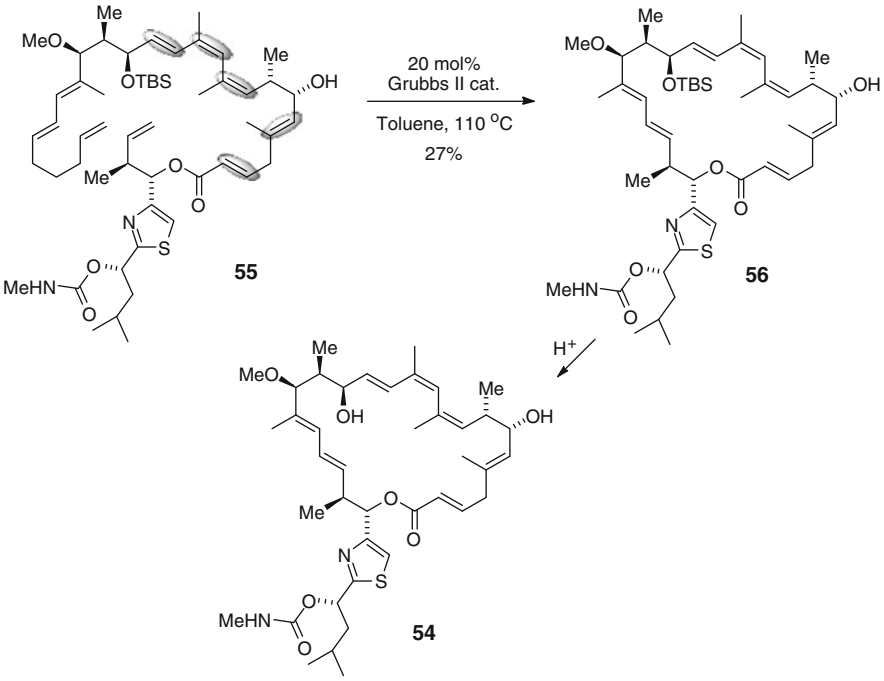


Fig. 17 Total synthesis of (−)-archazolid B (**54**) by Trauner et al.

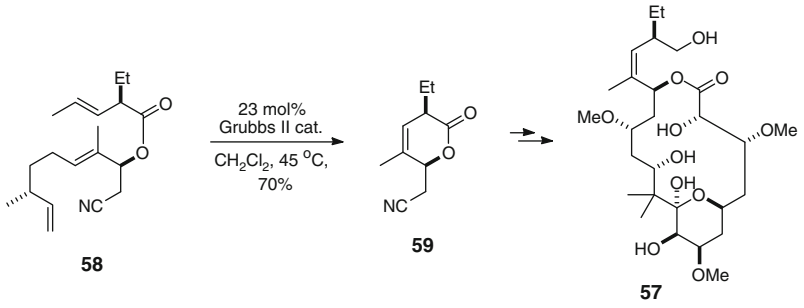


Fig. 18 Total synthesis of (+)-peloruside A (**57**) by Hoye et al.

Previous studies showed that the normal RCM reaction of simple triene (**61**) gave a poor regioselectivity to afford a mixture of five- and six-membered cyclic ethers. To resolve this problem, the authors tested a selective relay alkene RCM strategy, where the precursor (**62**) was modified to arm with an allyloxymethyl side chain. In this case, the initial ruthenium carbene species was selectively formed at the terminal alkene position of the allyloxymethyl side chain for both steric and electronic

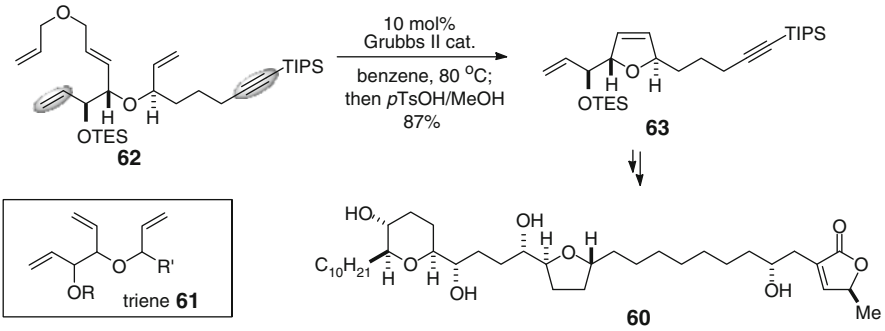


Fig. 19 Total synthesis of (−)-mucocin (**60**) by Crimmins et al.

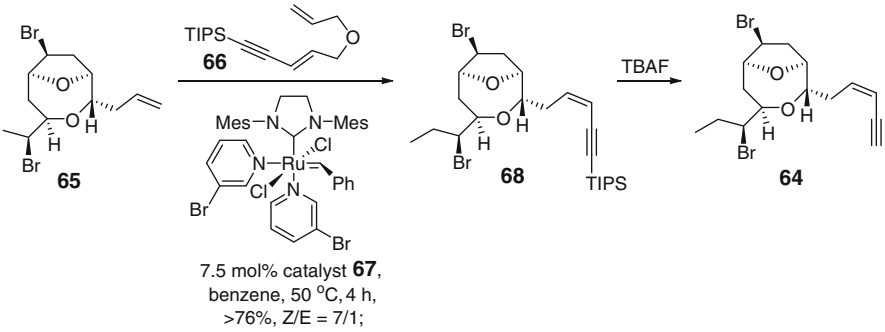


Fig. 20 Total synthesis of (+)-3-(Z)-isolaureatin (**64**) by Kim et al.

reasons, which further allowed the second metal carbene complex formed in the desired position to generate the five-membered cyclic ether (**63**).

The relay strategy has also been applied to selective alkene cross metathesis (CM). Very recently, Kim and coworkers reported the total synthesis of (+)-3-(*Z*)-isolaureatin (**64**) via this strategy (Fig. 20) [65]. The crucial cross metathesis of alkene for stereoselective introduction of the (*Z*)-enyne unit was successfully realized in 76% yield in the presence of Grubbs' catalyst (**67**) using Lee's protocol. The relay precursor, enyne (**66**), was subjected to the reaction mixture to initiate the desired process.

In summary, in this section we have reviewed some recent applications of relay olefin metathesis in the total synthesis of complex natural products. The collection of examples including both selective RRCM and relay cross metathesis demonstrates that the relay strategy has been broadly considered and implemented for complex natural product synthesis. The relay strategy will continue to provide possible solutions to the challenging synthesis where the limitations in classical metathesis methods are encountered.

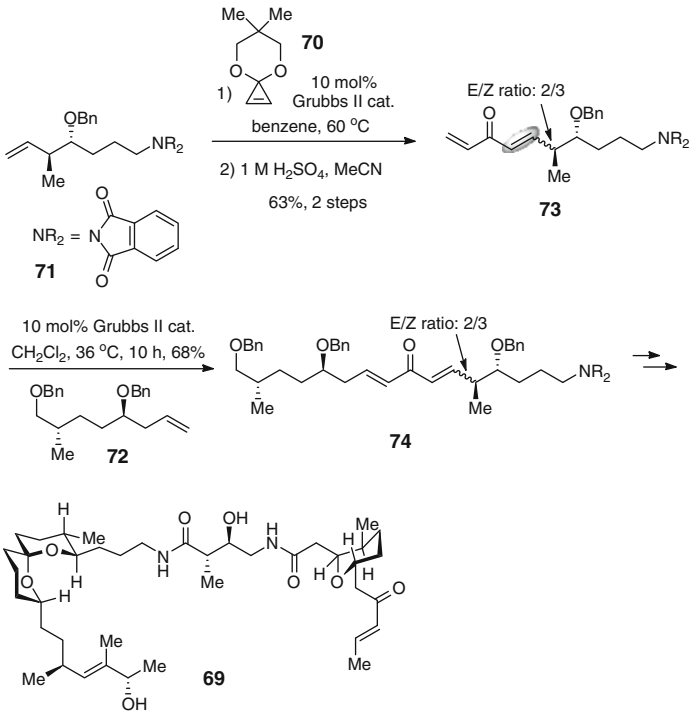


Fig. 21 Total synthesis of bistramide A (**69**) by Kozmin et al.

4 Selective Alkene Cross Metathesis

Selective alkene cross metathesis (CM) has played an important role in the general plan of complex natural product synthesis, where either the functionalization of terminal olefins attaching a side chain to the core skeleton, or coupling two fragments to construct the entire framework of the target molecule is required [66]. Herein, we select some significant and recent examples to highlight the successful applications of this strategy to natural product total synthesis.

In 2004, Kozmin et al. reported the total synthesis of bistramide A (**69**), a marine natural product with potent cytotoxicity [67]. In this synthesis (Fig. 21) the authors developed a novel approach featuring a sequential ring opening/selective alkene cross metathesis of highly strained cyclopropenone ketal (**70**) with terminal alkenes (**71**) and (**72**). After extensive reaction optimization, this process was successfully achieved using Grubbs II catalyst. For the cross metathesis reaction, a remarkable regioselectivity was observed in the presence of two different alkene moieties.

Anominine (**75**) is a unique and bioactive indole diterpenoid natural product isolated from the sclerotia of *Aspergillus* spp. [68]. The first total synthesis of (−)-anominine (**75**) was reported by Bonjoch and Bradshaw et al. [69]. In this study (Fig. 22) they employed a selective alkene cross metathesis reaction in the presence

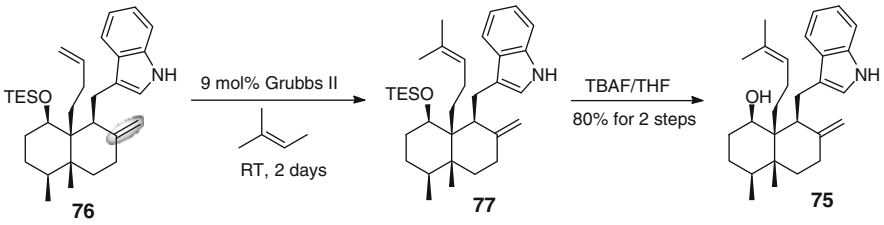


Fig. 22 Total synthesis of (−)-anominine (**75**) by Bonjoch and Bradshaw et al.

of two different olefin moieties at the late stage to install the required prenyl group. The high regioselectivity for CM is presumably attributed to the steric hindrance of the disubstituted methylene moiety.

An impressive example of selective alkene cross metathesis in a highly complex system was recently depicted by Phillips and coworkers (Fig. 23) [70]. In their studies toward the total synthesis of norhalichondrin B (**78**), an exceedingly challenging marine natural product with potent antitumor activity, they encountered a daunting task to couple selectively two highly functionalized fragments via alkene cross metathesis. Gratifyingly, this remarkable transformation was achieved in the presence of 20 mol% of the recently reported Grubbs' catalyst (**81**) to afford the desired cross-coupled product (**82**) in 62% yield.

The last example in this section is the total synthesis of RK-397 (**83**) by Sammakia et al. [71]. RK-397 (**83**) is an oxopolyene macrolide, which was isolated from a strain of soil bacteria. This natural product presents several synthetic challenges, including particularly the installation of the highly sensitive polyene moiety. Sammakia and coworkers successfully tackled this obstacle through a selective alkene cross metathesis reaction at a late stage (Fig. 24). By screening a number of reaction conditions, they found that treatment of alkene (**84**) and 2,4,6-hexatrienal with Grubbs I catalyst smoothly afforded polyene product (**85**) in 72% yield as a 4:1 mixture of *E*/*Z* isomers.

In summary, alkene cross metathesis has been successfully applied to numerous total syntheses of complex natural products. In most cases, this reaction can provide high yield, and good regio-, chemo-, and *E*-stereoselectivities. More importantly, the outcome of selective alkene cross metathesis can be predicted based on the propensity of different olefin for dimerization, making it a reliable transformation for design and implementation of complex natural product synthesis.

5 Selective Ene–Yne Ring Closing Metathesis

Ene–yne RCM is a very useful type of transformation where the double bond of ene–yne substrate is cleaved and a C–C bond is formed between the double and triple bonds, and the cleaved alkylidene component migrates to the alkyne moiety to generate a cyclized 1,3-diene product [72]. This reaction has recently been

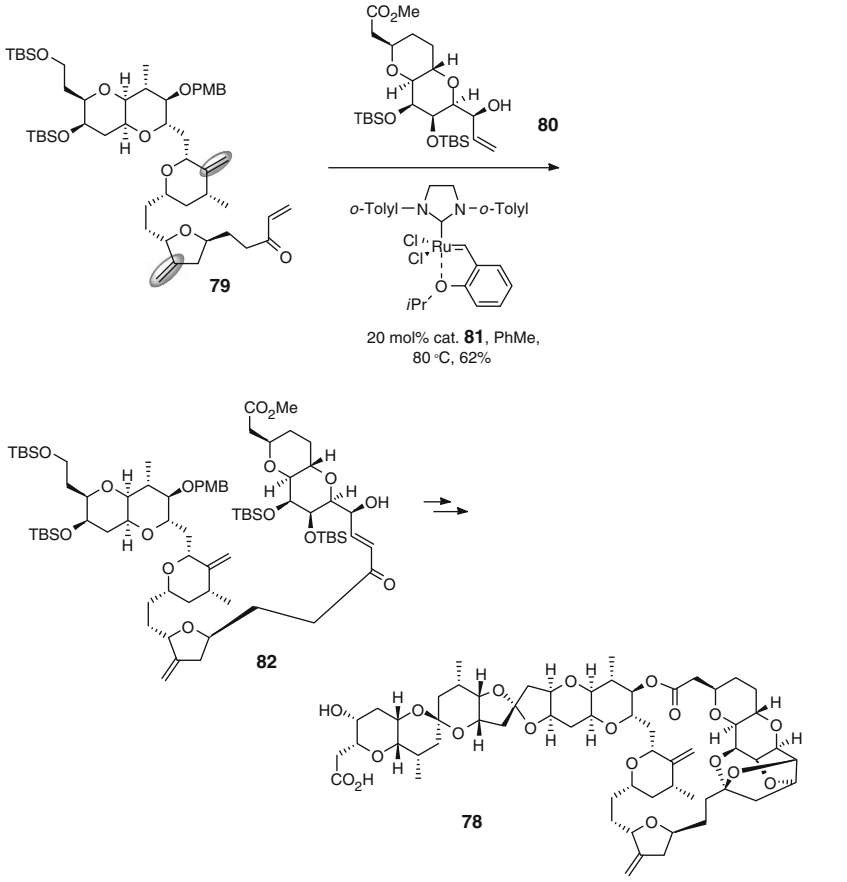


Fig. 23 Total synthesis of norhalichondrin B (**78**) by Phillips et al.

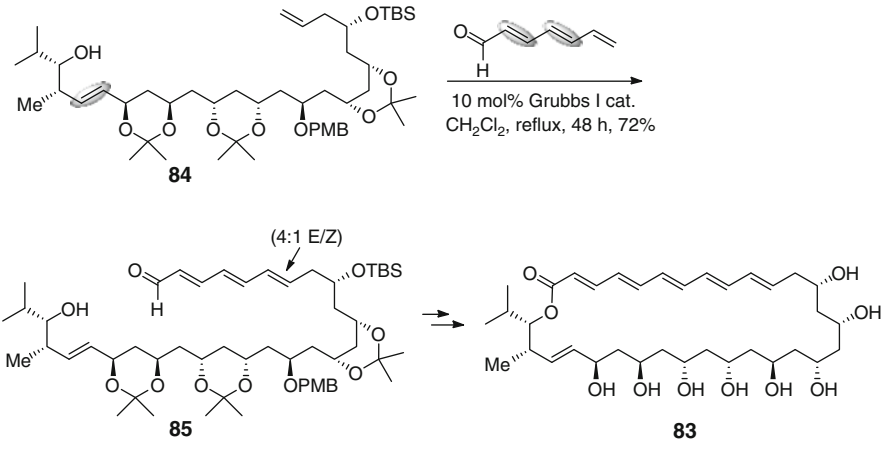


Fig. 24 Total synthesis of RK-397 (**83**) by Sammakia et al.

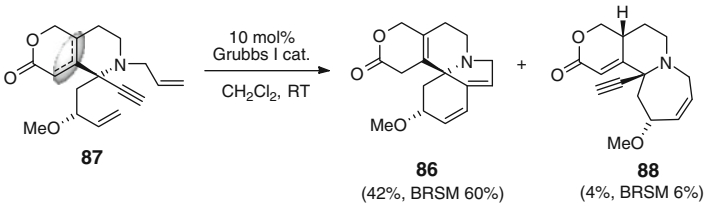


Fig. 25 Total synthesis of (+)-β-erythroidine (**86**) by Hatakeyama et al.

applied to the construction of complex polycyclic frameworks in natural product synthesis.

The *Erythrina* alkaloids have drawn broad attention from synthetic chemists owing to their intriguing chemical structures and promising biological activities. Recently, Hatakeyama and coworkers developed a novel approach to access efficiently the erythrinan skeleton, which relied on selective ene–yne RCM as a key step (Fig. 25) [73]. In their total synthesis of (+)-β-erythroidine (**86**), the trienyne precursor (**87**) was subjected to metathesis reactions in the presence of Grubbs I catalyst to afford the desired natural product (**86**) in 42% yield. This tandem sequence is highly regio-selective to form the 6/6/5/6 tetracyclic skeleton. The authors also indicated that Grubbs II catalyst was less effective and produced (+)-β-erythroidine (**86**) in less than 30% yield.

In 2008, Blechert et al. reported the total synthesis of *ent*-lepadin F (**89**) and G (**90**) by a tandem ene–yne–ene RCM [74]. Lepadins are members of marine alkaloids with decahydroquinoline framework. As a key step in their synthesis (Fig. 26) they planned to construct the decahydroquinoline core skeleton by a selective tandem ene–yne–ene RCM of the dienyne precursor (**91**). Conceivably, two different reaction pathways could be expected: (1) initiation of metathesis may occur at the terminal double bond followed by two consecutive RCMs to afford the desired 6/6 bicycle (**92**) or (2) initiation may occur on the disubstituted alkene followed by tandem RCMs to produce the undesired 5/7 bicycle (**93**). Considering the preference of initiation on monosubstituted double bond as well as the directing effect of free hydroxyl group, pathway (1) may be more favored. Gratifyingly, treatment of dienyne (**91**) with 10 mol% Grubbs I catalyst smoothly provided the desired 6/6 bicycle (**92**) in 90% yield.

In comparison with the previous examples, Metz and coworkers developed a similar strategy applying selective tandem ene–yne–ene RCM to assemble a 5/7 bicyclic framework [75]. In their total synthesis of sesquiterpene natural products (−)-clavukerin A (**94**) and (−)-isoclavukerin A (**95**) (Fig. 27), treatment of dienyne precursors (**96**) and (**97**) with phosphane-free Hoveyda–Blechert catalyst under an ethylene atmosphere cleanly afforded (−)-clavukerin A (**94**) and (−)-isoclavukerin A (**95**) in 53% and 55% yields, respectively. The high selectivity could also be explained by the preferential initiation of metathesis on the less substituted olefin in this tandem sequence. Similarly, Metz and coworkers utilized this tandem reaction in a more complex system to construct efficiently a 5/6/7/6 tetracyclic skeleton and

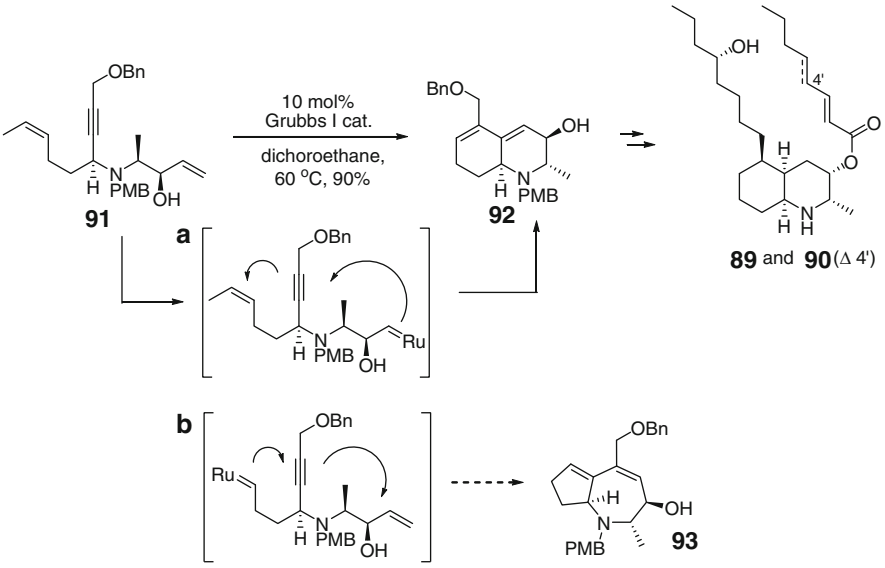


Fig. 26 Total synthesis of *ent*-lepadin F (**89**) and G (**90**) by Blechert et al.

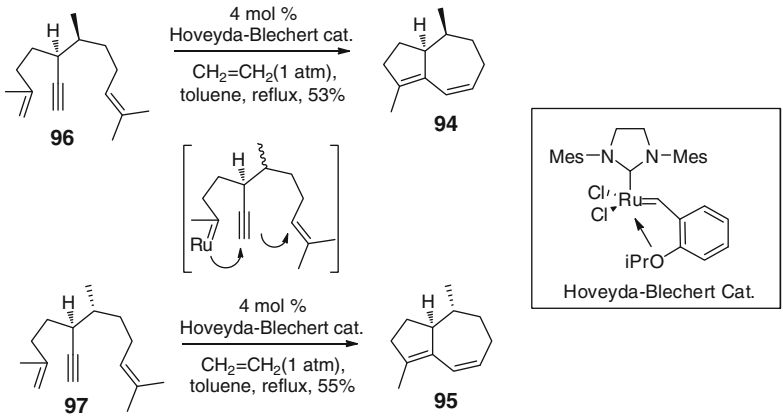


Fig. 27 Total synthesis of (−)-clavukerin A (**94**) and (−)-isoclavukerin A (**95**) by Metz et al.

accomplish the total syntheses of kempene-2 (**98**), kempene-1 (**99**), and 3-epi-kempene-1 (**100**) (Fig. 28) [76].

In summary, selective tandem ene–yne–ene RCM has proven to be a powerful means to construct highly functionalized polycyclic structures. Usually the regioselectivity could be achieved by the more favored cascade initiation on the less substituted alkene moiety as well as the effect of directing group. We envision this transformation will continue to offer synthetic chemists a useful tool for the synthesis of complex natural products.

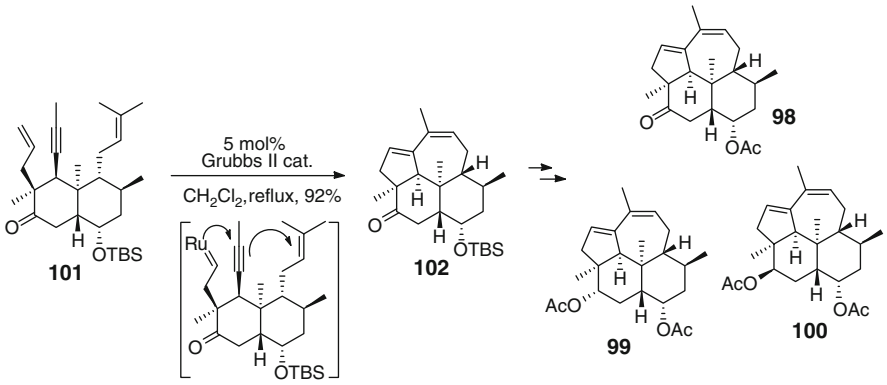


Fig. 28 Total synthesis of kempene-2 (**98**), kempene-1 (**99**), and 3-epi-kempene-1 (**100**) by Metz et al.

6 Cascade Reaction Involving Selective Alkene Metathesis

In the previous section we have shown that tandem ene–yne–ene RCM has been broadly used for the rapid and efficient construction of complex frameworks. In principle, selective alkene metathesis can be combined with other types of transformation to achieve a cascade reaction, which will provide a tremendous increase in molecular complexity [77]. Therefore, in this section, we highlight several recent examples of cascade reaction involving selective alkene metathesis for natural product synthesis.

In 2009, Lee and coworkers reported the concise total syntheses of epoxyquinoid natural products (+)-asperpentyn (**103**), (−)-harveynone (**104**), and (−)-tricholomenyn A (**105**) via cascade enyne metathesis and metallotropic [1,3]-shift (Fig. 29) [78]. In order to initiate the cascade effectively, a relay metathesis strategy was also adopted. By treatment of the polyenyne precursor (**106**) with Grubbs II catalyst, a mixture of epimers (**107**) and (**108**) was isolated in 62% yield. This cascade process selectively commenced from the terminal alkene of the allyl ether (**106**) to form the relay intermediate (**109**), which then underwent sequential relay metathesis and enyne metathesis to form alkynyl Ru-alkylidene (**111**). Subsequent facile metallotropic [1,3]-shift took place to provide the conjugated alkylidene product (**112**), which would ultimately deliver the final products (**107**) and (**108**) through termination at the less hindered carbon.

When ring opening metathesis (ROM) and RCM are sequentially combined, the cascade process is able to construct rapidly highly complex and functionalized structures. This methodology has proven its remarkable potential for the synthesis of complex natural product, as highlighted by a recent example reported by Phillips and Pfeiffer in their total synthesis of diterpenoid (+)-cyanthiwigin U (**115**) [79]. In this case, the required 7/6/5 tricyclic skeleton was effectively constructed by an elegant two-directional ROM–RCM cascade in the presence of Grubbs II catalyst

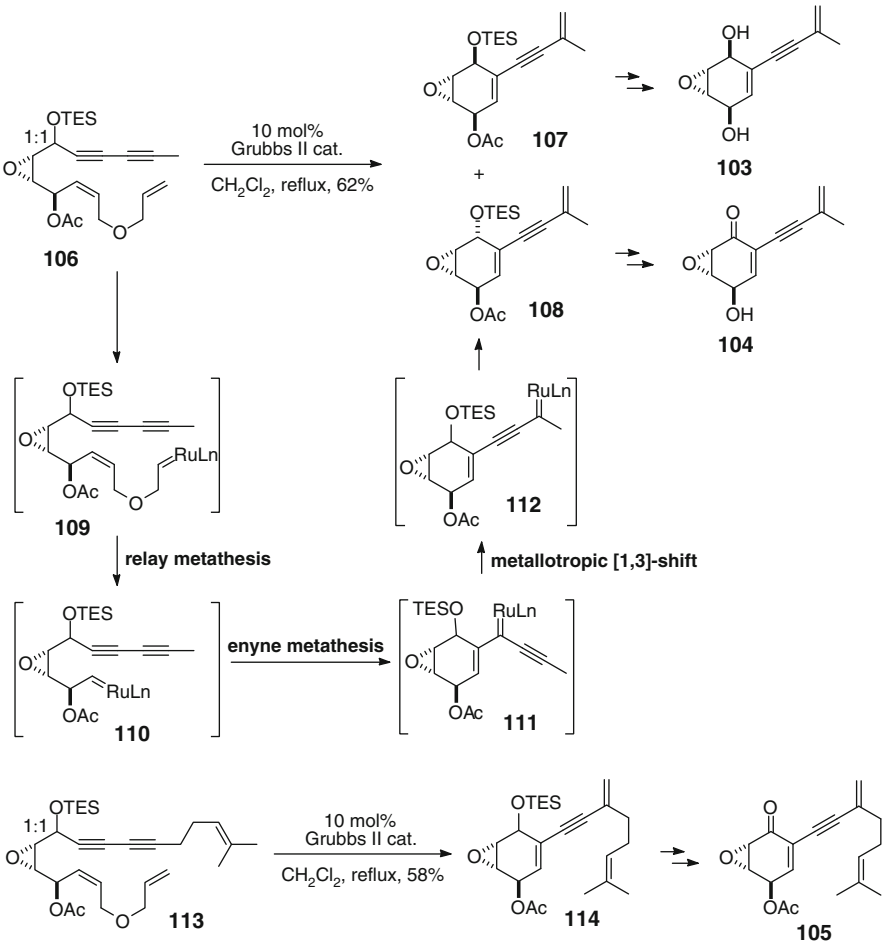


Fig. 29 Total synthesis of naturally occurring epoxyquinoids (+)-asperpentyn (**103**), (−)-harveynone (**104**), and (−)-tricholomenyn A (**105**) by Lee et al.

(Fig. 30). During this process, a high regioselectivity of two alkene RCM events was achieved.

In 2008, Stoltz and Enquist disclosed a novel approach to the total synthesis of the related cyathin diterpenoid (−)-cyanthiwigin F (**119**) [80]. They applied a simultaneous alkene RCM and cross metathesis (CM) protocol to achieve the required closure of the seven-membered ring as well as elaboration of the terminal allyl group (Fig. 31). This process was effectively and selectively conducted by treating polyene (**120**) with Grubbs–Hoveyda catalyst (**81**) and a vinyl boronate species to produce the desired bicycle (**121**) in 51% yield.

Phillips' laboratory also extended the domino process in natural product synthesis by combining ROM, RCM, and CM. For this cascade reaction, regioselectivity

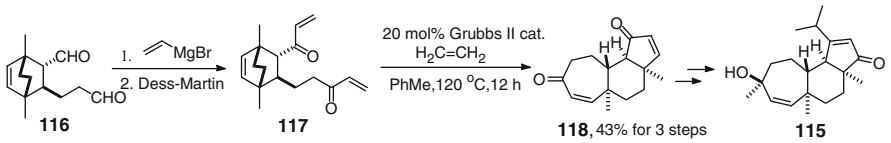


Fig. 30 Total synthesis of (+)-cyanthiwigin U (**115**) by Phillips and Pfeiffer

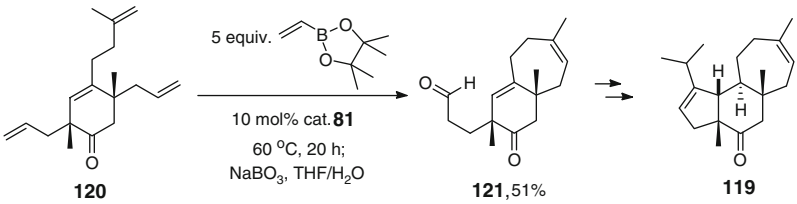


Fig. 31 Total synthesis of (−)-cyanthiwigins F (**119**) by Stolz and Enquist

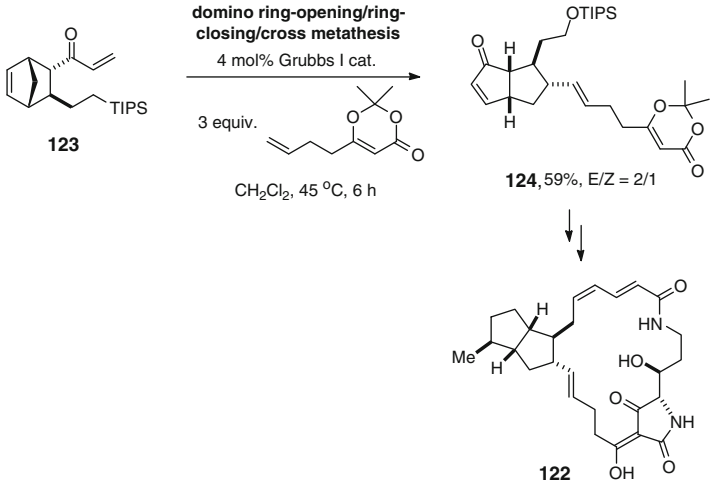


Fig. 32 Total synthesis of (+)-cylindramide A (**122**) by Phillips and Hart

is particularly important. In 2006, Phillips and Hart reported the total synthesis of marine natural product (+)-cylindramide A (**122**), where the key bicycle[3.3.0] octane ring system was successfully constructed by a cascade ROM–RCM–CM in the presence of Grubbs I catalyst (Fig. 32). During this process the high regioselectivity for alkene RCM and CM was observed [81].

When cascade reaction involving metathesis is applied in the complex natural product synthesis, proper sequence of multistage metathesis processes is crucial. The following example underscores this point. In 2006, Hoye and coworkers reported the total synthesis of (+)-gigantecin (**125**) [82]. In this work (Fig. 33)

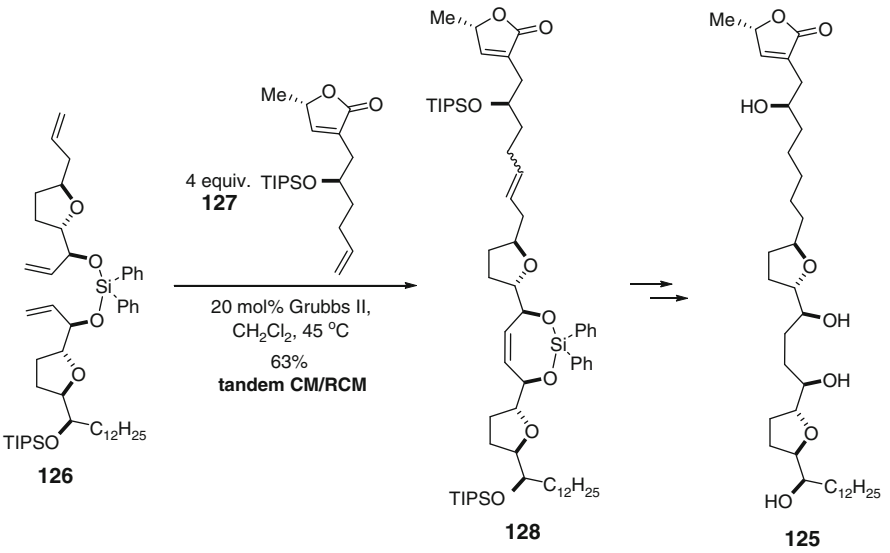


Fig. 33 Total synthesis of (+)-gigantecin (**125**) by Hoye et al.

they systematically studied the tandem ring closing/cross-metathesis sequence by changing the ordering of the RCM vs CM events. The authors found that in order to construct (+)-gigantecin (**125**) successfully, the order of the two metathesis reactions should be the "CM then RCM" sequence, otherwise an undesired skeleton was formed. As a result, the treatment of a mixture of triene (**126**) and alkene (**127**) (1:4 molar ratio) with Grubbs II catalyst smoothly provided the desired product (**128**) in 63% yield.

The tandem alkene metathesis reactions can also be combined with other types of transformation. One recent elegant example was reported by Mulzer and Ramharter et al. in their total synthesis of the *Lycopodium* alkaloid (+)-lycoflexine (**129**) (Fig. 34) [83]. Initially they conducted a tandem enyne/alkene RCM reaction to generate the key tricyclic diene (**131**). However, they observed that the yield of this cascade reaction was low, presumably due to the further decomposition of the labile diene (**131**) under this condition. Therefore they decided to attempt a tandem catalysis sequence and selectively hydrogenate the less-substituted alkene moiety in situ after the metathesis. As a result, the desired tricyclic product (**132**) was produced in 52% yield over three transformations.

The last example in this section is the application of a domino intramolecular enyne metathesis/cross metathesis reaction to the total synthesis of (+)-8-epi-xanthatin (**133**), which was reported by Martin and coworkers [84, 85]. In this study, the metathesis reactions are highly regioselective and leave the exomethylene moiety on the γ-lactone intact (Fig. 35).

In summary, the aforementioned examples have demonstrated the versatile utilities of the cascade reaction involving selective alkene metathesis and have

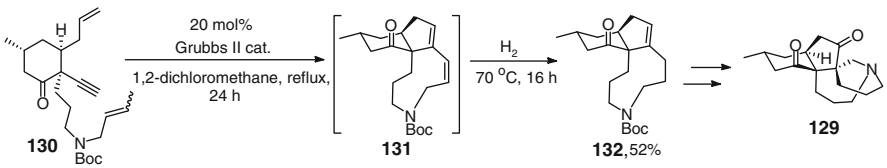


Fig. 34 Total synthesis of (+)-lycoflexine (**129**) by Mulzer and Ramharter et al.

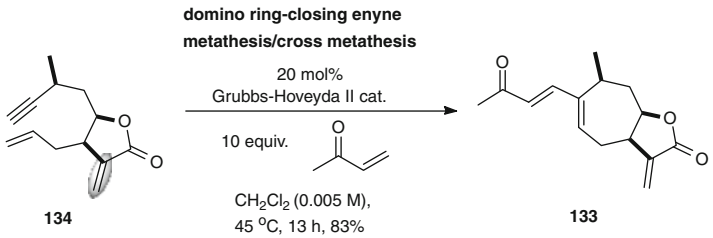


Fig. 35 Total synthesis of (+)-8-epi-xanthatin (**133**) by Martin et al.

explained how these domino processes allow for the rapid construction of complex and highly functionalized polycyclic frameworks. Given the tremendous advantages of metathesis cascade reactions in terms of catalytic efficiency and atom economy, we can only envision that more and more applications of this method in the total synthesis of complex natural product will arise in the future.

7 Catalytic Enantioselective Alkene Metathesis

Catalytic enantioselective alkene metathesis has recently been developed as a powerful method for the synthesis of complex natural products [86]. The availability of various chiral catalysts for olefin metathesis provides more flexible and concise means to construct efficiently highly functionalized and enantiomerically pure frameworks than using achiral catalytic complexes with chiral nonracemic substrates.

Hoveyda and Schrock's laboratories have pioneered in this field and developed a number of effective chiral Mo-based catalysts for enantioselective alkene metathesis [28]. A recent application of catalytic enantioselective alkene ROM/RCM in the total synthesis of (+)-africanol (**135**) was reported by Hoveyda et al. (Fig. 36) [87]. Treatment of *meso* tertiary TBS ether (**136**) with 3 mol% chiral alkylidene [Mo] catalyst (**137**) smoothly afforded the desired bicycle (**138**) in 97% yield and 87% ee.

Very recently, Hoveyda and coworkers reported a very elegant total synthesis of the *Aspidosperma* alkaloid (+)-quebrachamine (**139**) through a highly enantioselective alkene RCM promoted by molybdenum based catalyst (**141**) [88, 89]. In this study

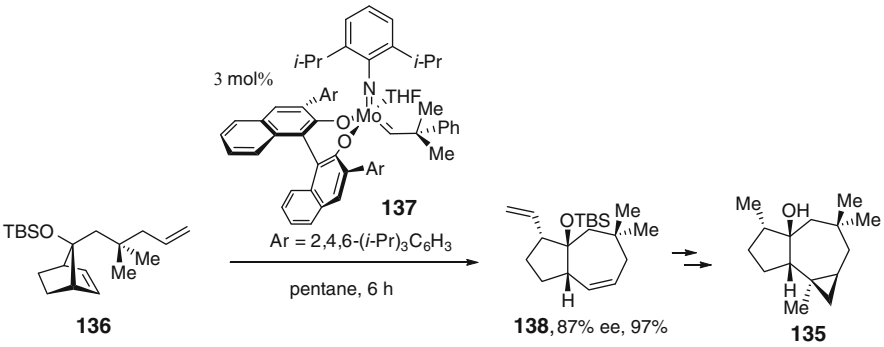


Fig. 36 Total synthesis of (+)-africanol (**135**) by Hoveyda et al.

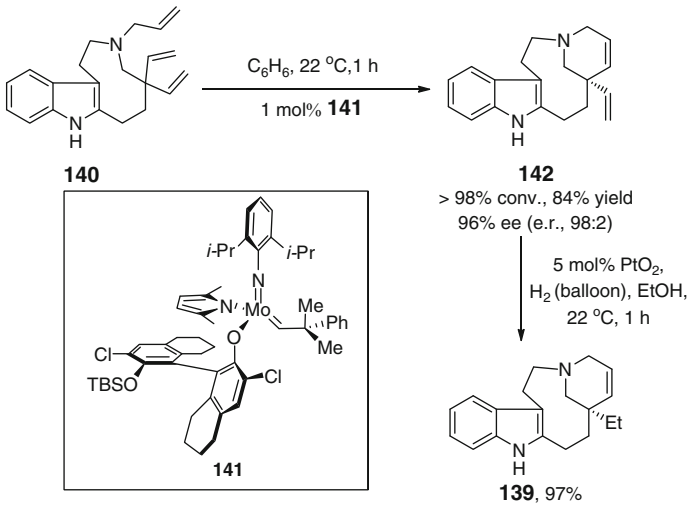


Fig. 37 Total synthesis of (+)-quebrachamine (**139**) by Hoveyda et al.

(Fig. 37), the late-stage enantioselective alkene RCM required the closure reaction onto one of two sterically hindered vinyl groups at a congested quaternary carbon in the presence of a potentially problematic tertiary amine moiety. Through an extensive screen of chiral catalysts, gratifyingly, the desired tetracycle (**142**) was obtained in 84% yield and 96% ee, which allowed the completion of total synthesis of (+)-quebrachamine (**139**).

In 2007, Hoveyda and Gillingham disclosed the total synthesis of (+)-baconipyrone C (**143**), which represents the first, and a rare example of, application of a Ru-catalyzed alkene ROM/RCM to complex natural product synthesis (Fig. 38) [90]. By treatment of oxabicycle (**144**) with 2 mol% chiral Ru carbene catalyst, the key highly functionalized pyran intermediate (**145**) was prepared in 63% yield and 88% ee. Notably, the chiral catalyst was generated in situ by subjection of

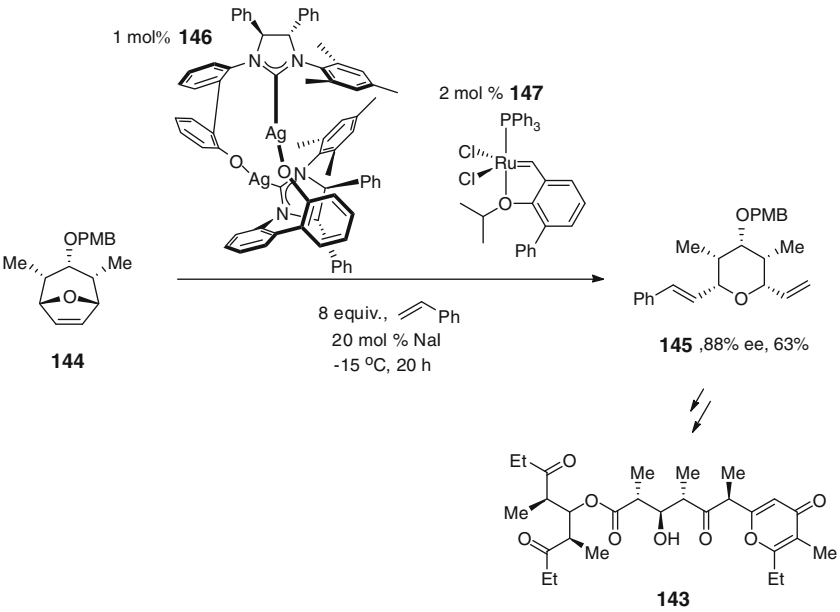


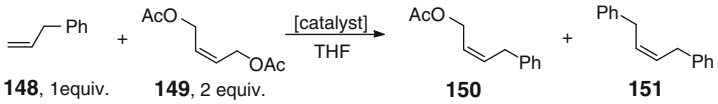
Fig. 38 Total synthesis of (+)-baconipyrone C (**143**) by Hoveyda and Gillingham

the Ag-based *N*-heterocyclic carbene (NHC) (**146**) with the achiral Ru-PCy_3 species (**147**) and NaI.

In summary, the development of catalytic enantioselective alkene metathesis has become a fascinating new direction for olefin metathesis. In this rapidly emerging field, several elegant applications in complex natural product synthesis have been reported to date. We can certainly expect that more active and robust catalysts will be developed and applied to target-oriented synthesis in the near future.

8 Catalytic *Z*-Selective Alkene Metathesis

Recently the new research direction of olefin metathesis has been focused on the development of a general method for *Z*-selective alkene metathesis. For alkene RCM, a variety of factors including substrate conformation, catalyst, temperature, solvent, etc., can determine the *Z*- or *E*-configuration of the final product, which makes the development of a general way to achieve *Z*-selectivity challenging. In addition, the *Z*-selective alkene cross metathesis (CM) has proved to be even more challenging, given that not only is it required that the reaction proceeds with minimal homocoupled byproduct but also it must exhibit a preference to produce the thermodynamically less favored stereoisomer. Grubbs and Hoveyda's laboratories have independently developed a number of catalytic systems with the intention of tackling these challenges.



148, 1equiv. **149**, 2 equiv. **150** **151**

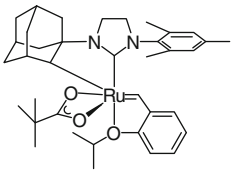
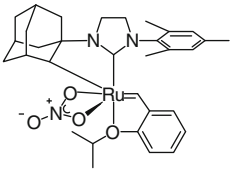
catalyst (loading, mol %)	time, h	temp, °C	conv to **150**, %	Z-**150**, %	conv to **151**,%	Z-**151**, %
 (**152**, 5 mol%)	9	70	37	89	26	96
	6	35	50	86	19	>95
 (**153**,1 mol%)	9	35	58	91	28	>95

Fig. 39 Improved ruthenium catalysts for Z-selective olefin metathesis by Grubbs et al.

Grubbs and coworkers studied a series of Ru-based catalysts and identified two lead catalysts for alkene cross metathesis that could provide the desired hetero-coupled product with high *Z*-selectivity for the resulting alkene moiety (Fig. 39) [91–93]. Comparably, Hoveyda and coworkers developed a number of Mo-based catalysts that enabled the selective synthesis of *Z*-alkenes [94, 95]. They successfully demonstrated that the novel molybdenum adamantylimido complexes (catalysts **154**–**156**) could promote ring opening/cross metathesis (ROCM) of oxabicycle (**157** or **158**) in good yield and excellent *Z*-selectivity (Fig. 40) [96]. These elegant studies paved the way to develop further more effective catalysts for *Z*-selective alkene metathesis and utilize these methods for the synthesis of complex natural products.

In 2011, Hoveyda et al. reported the total syntheses of two natural products, C18 (plasm)-16:0 (PC) (**162**) and KRN7000 (**163**), an anti-oxidant plasmalogen phospholipid and a potent immunostimulant, respectively, through catalytic *Z*-selective olefin cross metathesis (CM) [97]. In this study (Fig. 41), the corresponding disubstituted alkenes were efficiently formed in good yields and excellent *Z*-selectivity (up to >96%) by the treatment of a molybdenum alkylidene complex.

Very recently Hoveyda and coworkers disclosed another elegant study towards the synthesis of macrocyclic natural products through catalyst-controlled *Z*-selective RCM [98]. They developed an air-stable tungsten alkylidene species to promote efficient RCM of highly functionalized alkenes in useful yields with high *Z*-selectivity. This catalyst was utilized in the synthesis of complex natural products epothilone

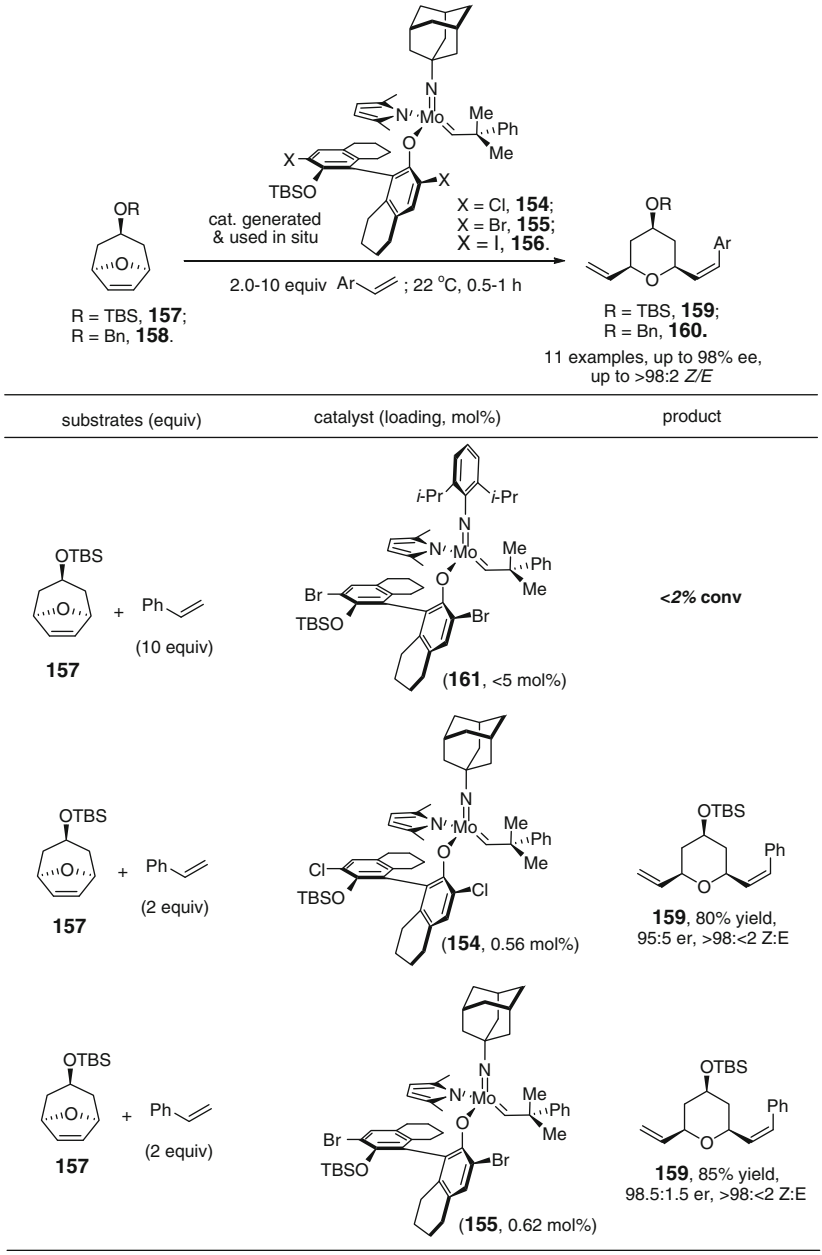


Fig. 40 Z- and enantioselective ring-opening/cross-metathesis reactions by Hoveyda et al.

C and nakadomarin A (**171**). The previous syntheses of these two natural products were all hindered by the late-stage, non-selective RCM to install the required *Z*-alkene moiety. The synthesis of nakadomarin A (**171**) is featured in Fig. 42. The key

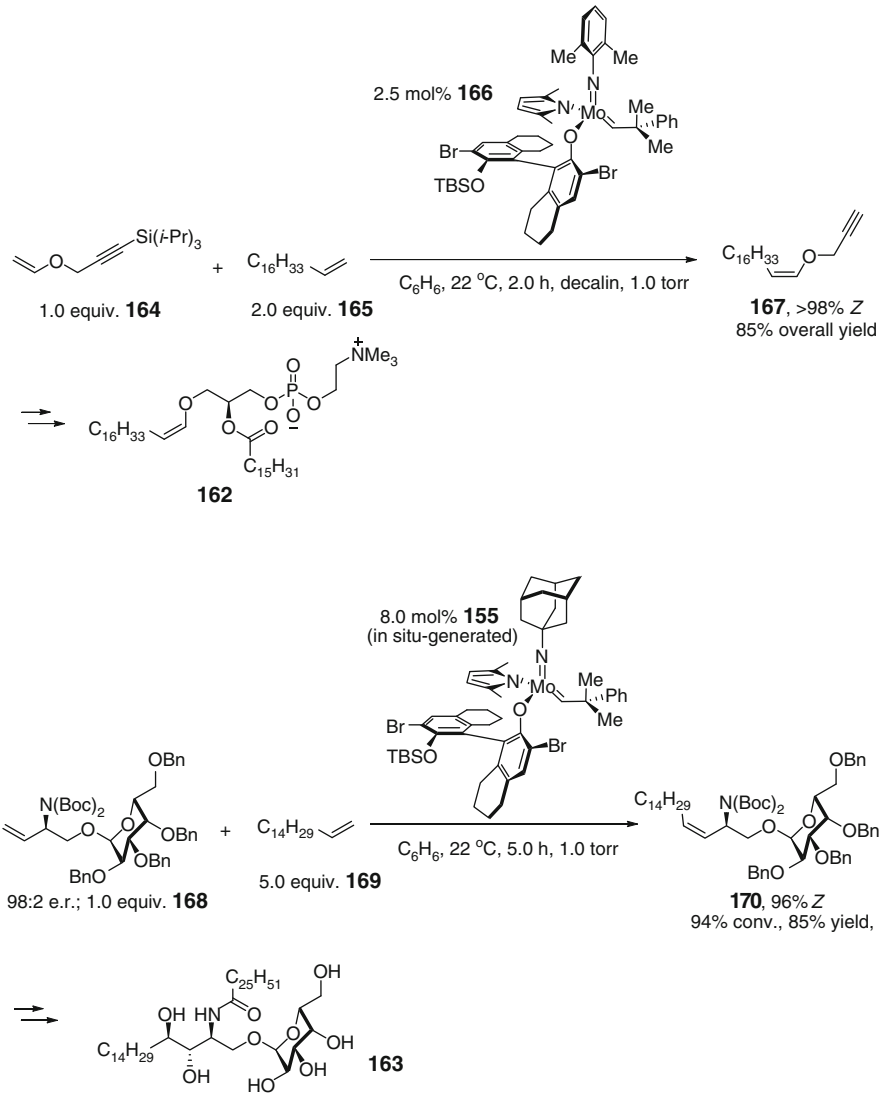
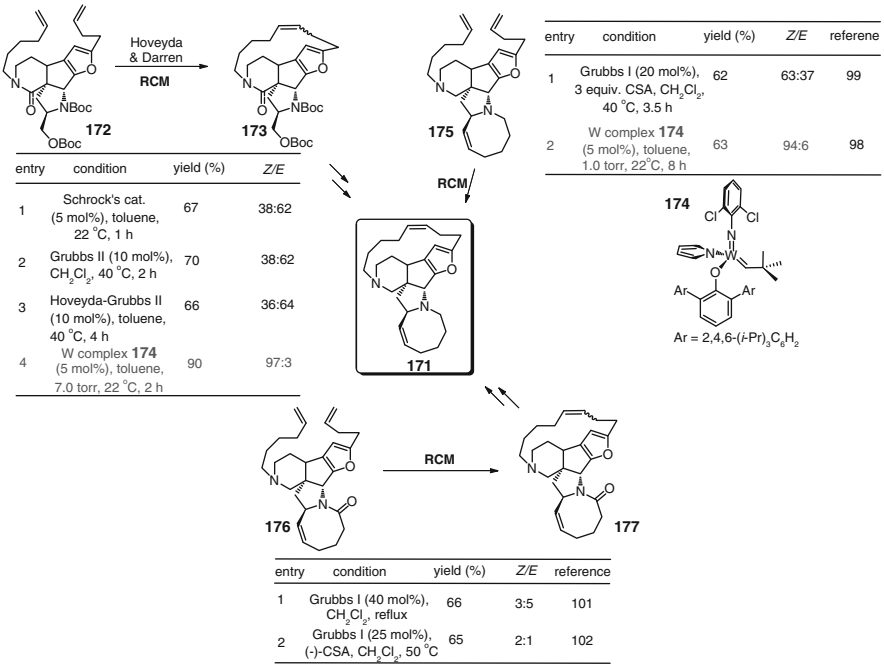


Fig. 41 Total syntheses of C18 (plasm)-16:0 (PC) (**162**) and KRN7000 (**163**) by Hoveyda et al.

intermediate (**173**) was prepared in 90% yield and with 97/3 *Z*/*E* selectivity in the presence of 5 mol% W complex (**174**). In contrast, reaction of (**173**) with other catalysts delivered lower yields and *Z*-selectivity. Alternatively, the W complex (**174**) could also be used successfully for the late-stage stereoselective RCM to generate the final natural product nakadomarin A (**171**) in good yield and excellent *Z*-selectivity. In comparison, all of the previous attempts for late-stage RCM using Ru-based catalysts provided much lower *Z*-selectivity [99–102].



entry	condition	yield (%)	*Z/E*
1	Schrock's cat. (5 mol%), toluene, 22 °C, 1 h	67	38:62
2	Grubbs II (10 mol%), CH_2Cl_2, 40 °C, 2 h	70	38:62
3	Hoveyda-Grubbs II (10 mol%), toluene, 40 °C, 4 h	66	36:64
4	W complex **174** (5 mol%), toluene, 7.0 torr, 22 °C, 2 h	90	97:3

entry	condition	yield (%)	*Z/E*	referene
1	Grubbs I (20 mol%), 3 equiv. CSA, CH_2Cl_2, 40 °C, 3.5 h	62	63:37	99
2	W complex **174** (5 mol%), toluene, 1.0 torr, 22°C, 8 h	63	94:6	98

entry	condition	yield (%)	*Z/E*	reference
1	Grubbs I (40 mol%), CH_2Cl_2, reflux	66	3:5	101
2	Grubbs I (25 mol%), (-)-CSA, CH_2Cl_2, 50 °C	65	2:1	102

Fig. 42 Z-Selective RCM strategy in total syntheses of nakadomarin A (**171**)

In summary, despite significant advances having been made in the field of olefin metathesis, a notable unresolved issue that limits its synthetic utility is the lack of efficient methods for *Z*-selective transformation. Recently there have been several elegant studies reported as shown in this section to resolve this challenge. We expect that more effective catalysts will be developed and applied to the synthesis of complex natural products in the near future.

9 Conclusions

We have witnessed the remarkable advance of selective alkene metathesis reactions over the last a few years. Many synthetic chemists have utilized this reaction as a very practical, versatile, and selective synthetic tool to prepare complex molecules including natural products. Selective alkene metathesis has helped to elevate the art and science of natural product total synthesis to its present high level. However, many critical discoveries in catalytic alkene metathesis, particularly the development of more effective catalysts that are easily obtained and able to provide excellent selectivities, remain to be made. It has been delightful to review this field and highlight some of the most significant and exciting examples of recent applications of selective alkene metathesis in the total synthesis of complex natural

products. We sincerely hope this review will provide useful information for synthetic chemists and stimulate new developments and applications of selective alkene metathesis reactions in the field of natural product synthesis.

Acknowledgements Financial support of this work from Program for New Century Excellent Talents in University (NCET-10-0614) and National Natural Science Foundation of China (20802050, 21072150) is gratefully acknowledged.

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Top Curr Chem (2012) 327: 197–238
DOI: 10.1007/128_2012_314

Published online: 28 February 2012

Olefination Reactions of Phosphorus-Stabilized Carbon Nucleophiles

Yonghong Gu and Shi-Kai Tian

Abstract A range of phosphorus-stabilized carbon nucleophiles have been employed for alkene synthesis with high chemo-, regio-, and stereoselectivity. The Wittig, Horner–Wadsworth–Emmons, Horner–Wittig, and Evans–Akiba reactions utilize phosphonium-, phosphonate-, phosphine oxide-, and pentacoordinated phosphorane-stabilized carbanions as nucleophiles, respectively, to undergo olefination with aldehydes or ketones, and each of these transformations has its own advantages and limitations. Modifying the structures of these nucleophiles along with optimizing reaction conditions results in the formation of a wide variety of polysubstituted alkenes in a highly stereoselective manner. The olefination of imines with phosphonium ylides has recently emerged as a useful approach to tune the stereoselectivity for alkene synthesis. This review focuses on recent advances in the stereoselective olefination of phosphorus-stabilized carbon nucleophiles.

Keywords Aldehydes · Alkenes · Imines · Ketones · Phosphorus

Contents

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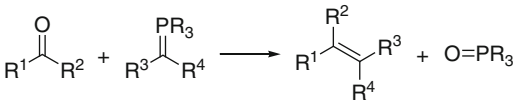
1 Introduction

Stereodefined alkenes are ubiquitous structural motifs in many natural products and pharmaceutics, and, moreover, they serve as a foundation for a broad range of chemical transformations. Nowadays, carbonyl olefination, elimination, alkyne addition, alkenylation, and alkene metathesis constitute the most widely used methods for the stereoselective synthesis of various alkenes [1–3]. Whereas no single method provides a universal solution to stereoselective alkene synthesis, the olefination reactions of aldehydes and ketones with phosphorus-stabilized carbon nucleophiles have enjoyed widespread prominence and recognition owing to their simplicity, convenience, complete positional selectivity, and generally high levels of geometrical control [4–9].

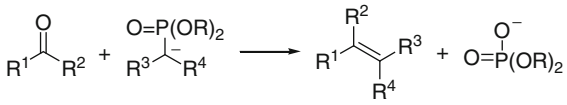
A few types of phosphorus-stabilized carbon nucleophiles have been extensively studied for stereoselective alkene synthesis (Scheme 1). Carbonyl olefination with a phosphonium ylide is referred to as the Wittig reaction, named after Georg Wittig who first disclosed this transformation in 1953 [10]. Since its inception, this reaction has received numerous modifications with regard to the structures of the phosphorus-stabilized carbon nucleophiles. Three important variants, the Horner-Wadsworth-Emmons, Horner-Wittig, and Evans–Akiba reactions, have been evolved using phosphonate-, phosphine oxide-, and pentacoordinated phosphorane-stabilized carbanions as nucleophiles, respectively. Such modifications significantly extend the scope of stereoselective alkene synthesis. A distinct strategy to modify the Wittig reaction is to employ imines rather than carbonyl compounds as electrophiles, and the stereoselectivity for alkene synthesis can be significantly enhanced by tuning the electronic and steric properties of the substituents on the imine nitrogen atoms.

Each of these transformations has its own advantages and limitations, and the selection of an appropriate method is essential for a desired stereoselective alkene synthesis. In this chapter we would like to discuss briefly the general stereochemical trends and focus on recent developments in the field of olefination reactions based on these phosphorus-stabilized carbon nucleophiles.

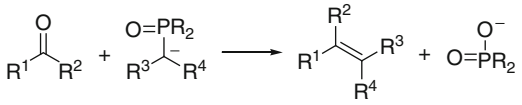
a The Wittigreaction



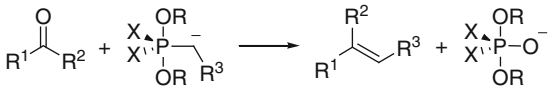
b The Horner-wadsworth-Emmons reaction



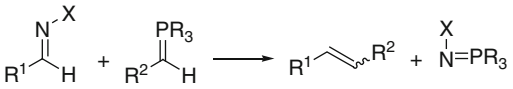
c The Horner-Wittig reaction



d The Evans-Akiba reaction



e Olefination of imines with phosphonium ylides



Scheme 1 Olefination reactions of phosphorus-stabilized carbon nucleophiles

2 The Wittig Reaction

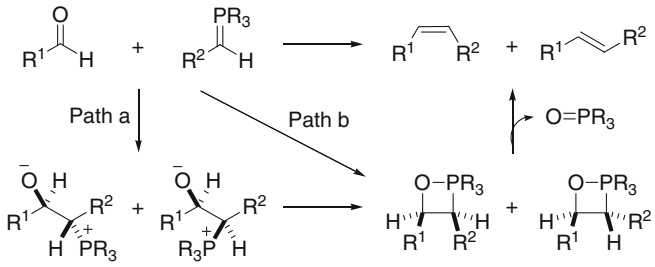
The employment of phosphorus-stabilized carbon nucleophiles for alkene synthesis was initiated by the discovery of the Wittig reaction [10], which provides a convenient method for the preparation of a wide variety of polysubstituted alkenes with complete positional selectivity and generally high levels of geometrical control. Moreover, the phosphonium ylides used in the Wittig reaction are readily formed by the addition of suitable bases to the corresponding phosphonium salts, which are commonly prepared by treating alkyl halides with phosphines.

2.1 Mechanism

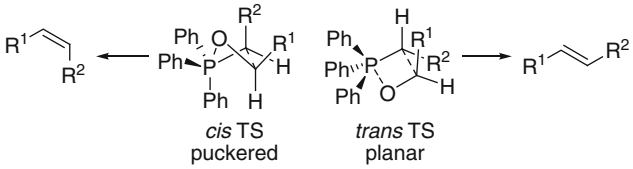
The Wittig reaction was originally thought to occur in three steps: (1) nucleophilic addition of the phosphonium ylide to the aldehyde (or ketone) to give a betaine; (2) carbon–carbon bond rotation of the betaine to form an oxaphosphetane; and (3) decomposition of the oxaphosphetane to yield an alkene and a phosphine oxide (Scheme 2, Path a). Oxaphosphetanes have been detected by low-temperature ^{31}P, ^{1}H, and ^{13}C NMR spectroscopic analysis of the reaction mixtures of carbonyl compounds with nonstabilized (R^2 = alkyl) or semistabilized (R^2 = aryl) phosphonium ylides [11–15]. Similar observance is not successful with stabilized phosphonium ylides (R^2 = alkoxycarbonyl, acyl). Although oxaphosphetanes are generally unstable and decompose readily into alkenes and phosphine oxides upon warming to room temperature, several stable oxaphosphetanes have been identified unambiguously by single crystal X-ray analysis [16–21]. In contrast, betaines have never been observed spectroscopically under salt-free Wittig reaction conditions (i.e., in the absence of lithium ions) and in some cases they have even been excluded [22]. Nevertheless, betaines have been observed sometimes in the Wittig reaction in the presence of strongly coordinating ions such as lithium ion [23, 24].

It is now accepted that the oxaphosphetane intermediate is formed directly by a [2+2] cycloaddition of the phosphonium ylide with the aldehyde (or ketone) through a four-center transition state, in which the formation of the carbon–carbon bond is more advanced than that of the phosphorus–oxygen bond (Scheme 2, Path b). Although there are some exceptions [25, 26], the oxaphosphetane formation step is generally nonreversible [27, 28] and decides the stereoselectivity.

The stereochemical outcome of the Wittig reaction is believed to be the result of steric effects that develop as the phosphonium ylide and the aldehyde approach one another. A few transition state models have been proposed by Schlosser [29], McEwen [30, 31], and Vedejs [27, 28, 32]. Among them, the Vedejs model best accounts for the stereoselectivity on the basis of an interplay of 1,2- and 1,3-steric interactions in the four-center transition state (Scheme 3). The addition of the nonstabilized phosphonium ylide to the aldehyde proceeds through an early transition state that is fairly flexible. A preferred geometry for the *cis* transition state is



Scheme 2 Mechanisms of the Wittig reaction



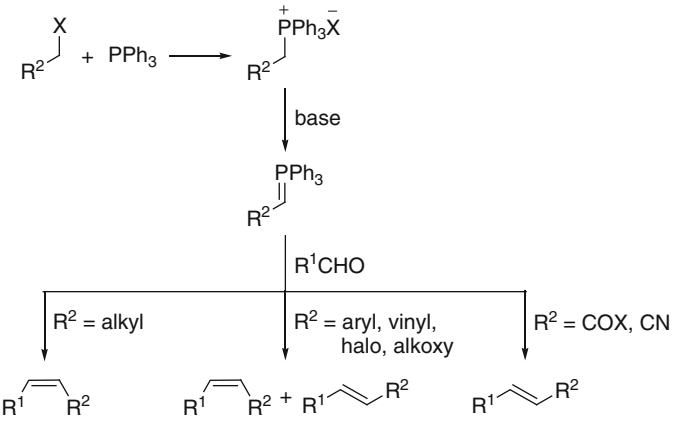
Scheme 3 Transition state structures according to the Vedejs model

puckered due to the relief of steric interactions between the ylide substituent and the aldehyde substituent (1,2-interaction) and between the aldehyde substituent and the phosphorus substituents (1,3-interaction). On the other hand, a preferred geometry for the *trans* transition state is planar because puckering to relieve 1,3-interactions would increase 1,2-interactions. The balance of steric effects favors the *cis* transition state that leads to a *Z*-alkene. In contrast, the reaction of the stabilized phosphonium ylide with the aldehyde proceeds through a late transition state that is less flexible and constrained to be closer to be planar. Since the *cis* transition state suffers from serious 1,2-interactions, the *trans* one is favored and the reaction preferentially gives an *E*-alkene.

According to the density functional theory (DFT) calculations of the salt-free Wittig reaction performed by Aggarwal and Harvey et al. [33, 34], the puckering ability of the transition states in the Vedejs model does not depend on ylide stabilization. In the case of nonstabilized and semistabilized phosphonium ylides, the geometry of the transition states is decided by an interplay of 1,2-, 1,3-, and C-H···O interactions. In contrast, a dipole-dipole interaction governs the transition state structures for stabilized phosphonium ylides.

2.2 Scope and Limitations

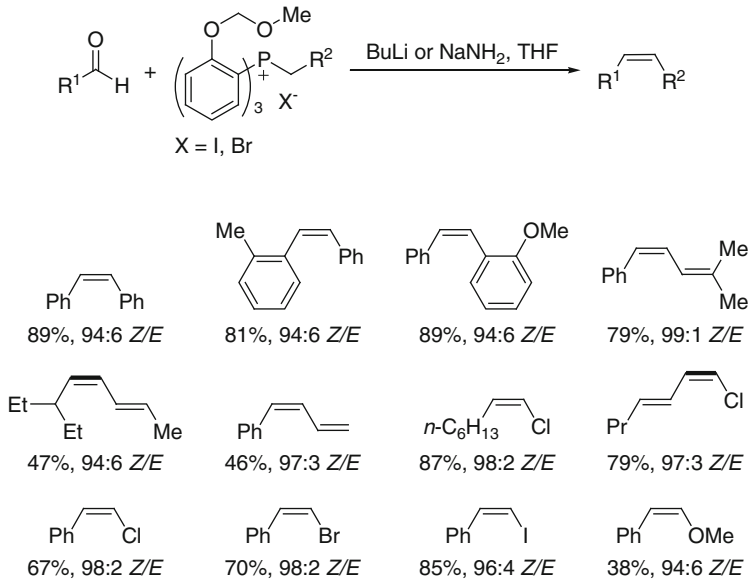
Triphenylphosphonium ylides ($Ph_3P{=}CHR^2$) are employed most frequently in the Wittig reaction because they are readily prepared through the reaction of triphenylphosphine, which is inexpensive and air-stable, with alkyl halides followed by treatment of the resulting phosphonium salts with suitable bases (Scheme 4). Nonstabilized (R^2 = alkyl) and semistabilized (R^2 = aryl, vinyl, halo, alkoxy) triphenylphosphonium ylides are very reactive and unstable toward moisture and oxygen, and hence they are prepared in situ at low temperature (usually at −78 °C) in an etheral solvent (e.g., tetrahydrofuran, diethyl ether, or 1,2-dimethoxyethane) under nitrogen (or argon) in the presence of a strong base such as BuLi, $NaNH_2$, lithium diisopropylamide (LDA), sodium hexamethyldisilylamide (NaHMDS), or KOBu-*t*. In contrast, stabilized triphenylphosphonium ylides (R^2 = alkoxycarbonyl, acyl, cyano) are less reactive and usually isolable, and their preparation often requires a weaker base such as aqueous NaOH.



Scheme 4 Preparation of phosphonium ylides and general stereochemical outcomes of the Wittig reaction

A wide variety of aldehydes and ketones are effective substrates for the Wittig reaction, and in most cases mono-, di-, and trisubstituted alkenes are prepared in good yields. Additives (e.g., lithium salts [35, 36], carboxylic acids [37, 38], phase transfer catalysts (PTC) [39], cyclodextrins [40], and silica gel [41]), elevated temperature [42], high pressure [43, 44], microwave irradiation [45–48], light irradiation [49], sonication [50], ionic liquids [51], water [52–54], supercritical CO_2 [55], and solvent-free conditions [56] have been utilized in some cases to improve the yields, stereoselectivity, manipulations, and environmental impacts. The Wittig reaction tolerates a range of functional groups such as hydroxy, amino, halo, aromatic nitro, ester, amide, and cyano groups. The stereochemistry of the Wittig reaction is governed primarily by the nature of the phosphonium ylide, though it is affected more or less by a few other variables such as the base used for ylide formation, ion, solvent, and temperature. In general, the Wittig reaction yields preferentially *Z*-alkenes for nonstabilized triphenylphosphonium ylides under salt-free conditions, and *E*-alkenes for stabilized triphenylphosphonium ylides, but mixtures of *Z*- and *E*-alkenes for semistabilized triphenylphosphonium ylides (Scheme 4).

It is a powerful strategy to tune stereoselectivity in the Wittig reaction by modifying the *P*-phenyl groups of triphenylphosphonium ylides albeit their preparation requires extra synthetic manipulations. In this regard, extensive studies have shown that the employment of ortho-substituted aryl groups on the ylide phosphorus atoms is able to modulate stereoselectivity significantly [57–60]. In particular, this strategy is effective in enhancing *Z* selectivity for the Wittig reaction with semistabilized phosphonium ylides. As reported by Schlosser et al., the use of semistabilized tris(2-methoxymethoxyphenyl)phosphonium ylides leads to high *Z* selectivity in the synthesis of stilbenes [61], conjugated dienes [62], alkenyl halides, and vinyl ethers [63] (Scheme 5).

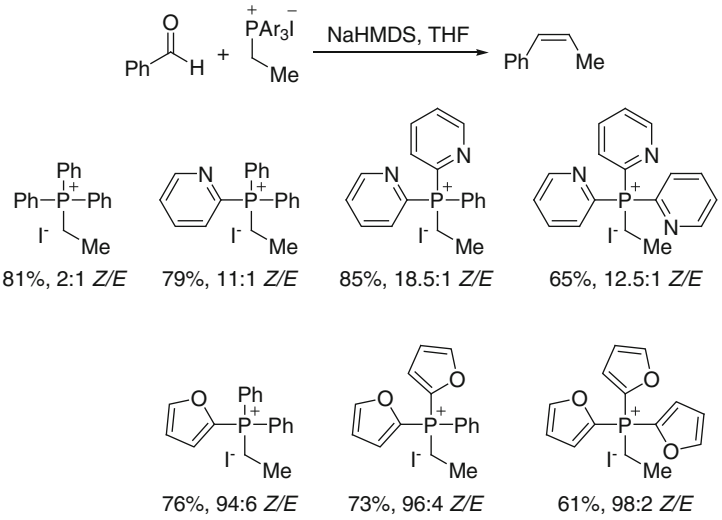


Scheme 5 Wittig reaction of semistabilized tris(2-methoxymethoxyphenyl)phosphonium ylides

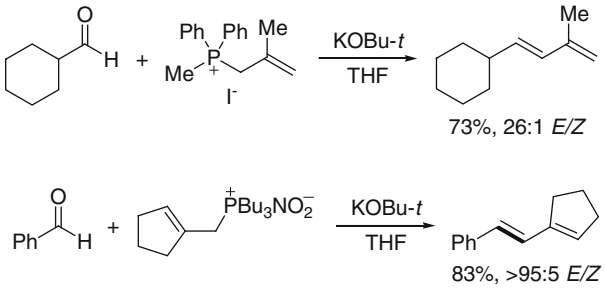
The introduction of *P*-heteroaryl groups to nonstabilized phosphonium ylides can significantly enhance *Z* selectivity in the Wittig reaction. Berger et al. have found that replacement of the *P*-phenyl groups of nonstabilized triphenylphosphonium ylides with 2-pyridinyl or 2-furyl groups leads to a dramatic increase in *Z* selectivity in the corresponding Wittig reaction using NaHMDS to generate the phosphonium ylides (Scheme 6) [21, 64]. However, the yield is dramatically decreased when BuLi is used as the base. The formation of a betaine salt adduct as the intermediate has been proposed to suppress the oxaphosphetane formation during the Wittig reaction.

In sharp contrast, *E* selectivity has been achieved by replacing the *P*-phenyl groups of semistabilized triphenylphosphonium ylides with simple alkyl groups. Such phosphonium ylides are prepared by treatment of their corresponding phosphonium salts with an appropriate base because of the excellent chemoselectivity for deprotonation at the benzylic or allylic position over at the alkyl position. Notably, high *E* selectivity has been achieved for the newly formed double bond in the Wittig reaction of either an allylidenemethyldiphenylphosphorane [65] or an allylidenetributylphosphorane (Scheme 7) [66, 67].

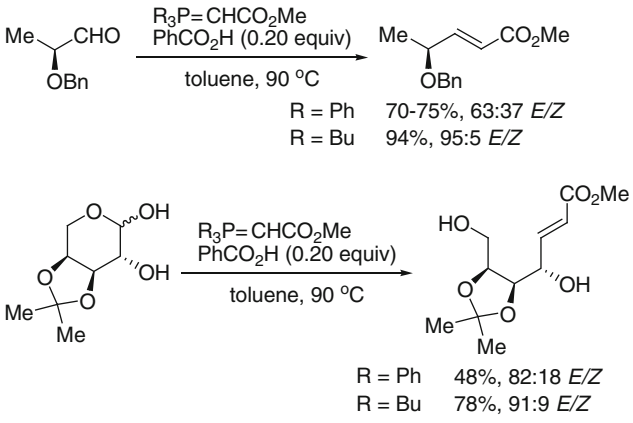
This strategy has been extended to the Wittig reaction of stabilized phosphonium ylides. In general, low *E* selectivity has been obtained from the Wittig reaction of (alkoxycarbonylmethylene)triphenylphosphoranes with α-alkoxy aldehydes or sugar lactols. Nevertheless, Martin et al. have found that the reaction of (methoxycarbonylmethylene)tributylphosphorane with α-alkoxy aldehydes or sugar lactols proceeds smoothly in the presence of a catalytic amount of benzoic acid to give α,β-unsaturated esters in high yields and *E* selectivity (Scheme 8) [68].



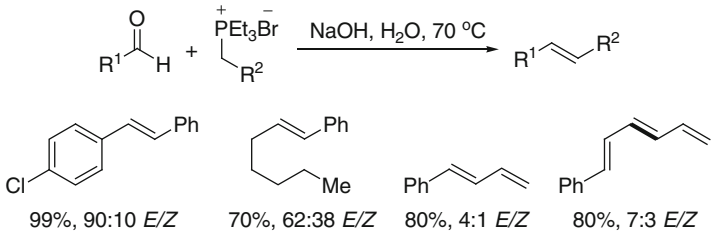
Scheme 6 Wittig reaction of nonstabilized phosphonium ylides bearing *P*-heteroaryl groups



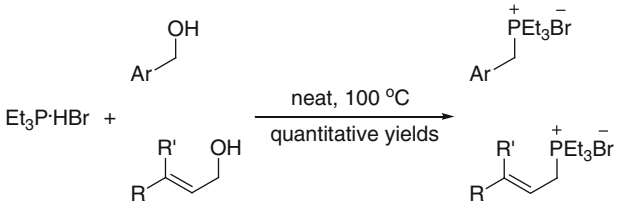
Scheme 7 Wittig reaction of semistabilized phosphonium ylides bearing *P*-alkyl groups



Scheme 8 Wittig reaction of stabilized phosphonium ylides



Scheme 9 Wittig reaction of semistabilized triethylphosphonium ylides



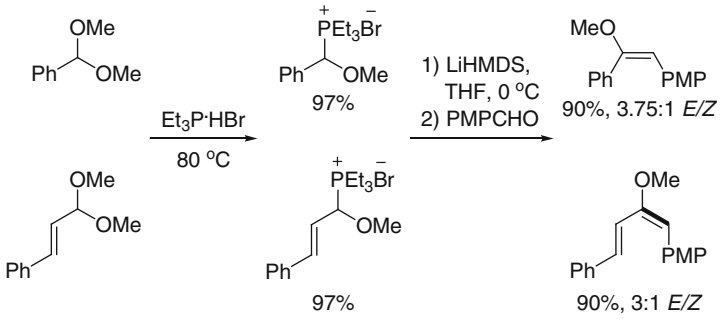
Scheme 10 Preparation of benzyltriethyl- and allyltriethylphosphonium salts

Recently, benzylidenetriethylphosphoranes and allylidenetriethylphosphoranes have been reported by McNulty et al. to be generated chemoselectively from their corresponding phosphonium salts in water using NaOH or LiOH as the base (Scheme 9) [69, 70]. These semistabilized phosphonium ylides react with aldehydes to give conjugated alkenes with moderate to good *E* selectivity. It is noteworthy that the triethylphosphine oxide byproduct is water-soluble and hence is readily removed from the process by simple extraction.

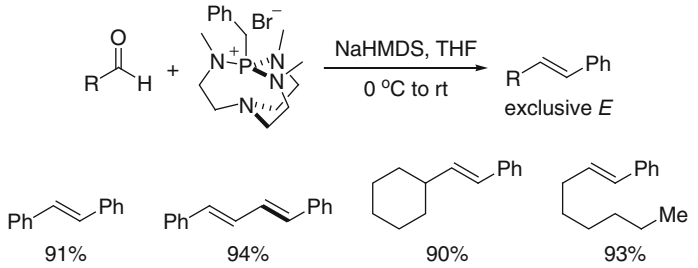
Benzyltriethyl- and allyltriethylphosphonium salts are usually prepared by direct substitution of benzylic and allylic halides with triethylphosphine, respectively. However, triethylphosphine is sensitive to air. McNulty et al. have found that these phosphonium salts can be formed in quantitative yields through the reaction of air-stable triethylphosphine hydrobromide with allylic or benzylic alcohols, which are more readily accessible and less reactive than their halide counterparts (Scheme 10) [71].

A similar procedure has been applied to the preparation of α-methoxy phosphonium salts in high yields from triethylphosphine hydrobromide and dimethyl acetals (Scheme 11) [72]. The resulting phosphonium salts are subjected to ylide formation/olefination to afford a range of vinyl ethers and functionalized 1,3-dienes with moderate *E* selectivity.

It is interesting to replace the *P*-phenyl groups of triphenylphosphonium ylides with dialkylamino groups in the Wittig reaction. Verkade et al. have examined the Wittig reaction of $PhCH{=}P(MeNCH_2CH_2)_3N$ with a range of aldehydes (Scheme 12) [73, 74]. This reaction proceeds at relatively high temperature (0 °C to room temperature) to give alkenes with exclusive *E* selectivity. In contrast with



Scheme 11 Preparation and olefination of α-methoxy phosphonium salts

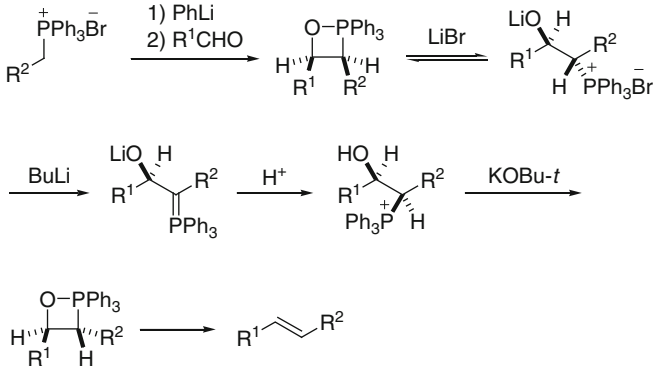


Scheme 12 Olefination of $PhCH{=}P(MeNCH_2CH_2)_3N$

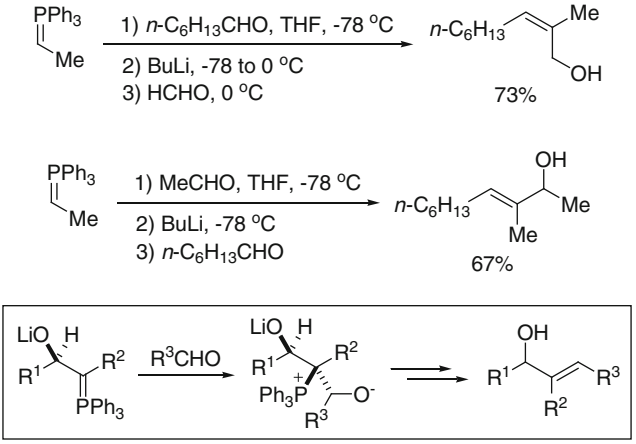
commonly used phosphonium ylides, the *E* selectivity is maintained despite changes in the metal ion of the ionic base used for ylide formation, temperature, and solvent polarity.

2.3 The Schlosser Modification

The Schlosser modification of the Wittig Reaction allows the formation of an *E*-alkene by delaying normal elimination of a phosphine oxide from the initially formed oxaphosphetane intermediate through employment of excess soluble lithium salts and an organolithium (preferably PhLi) at low temperature (Scheme 13) [75–78]. The lithium salt can promote ring opening of the oxaphosphetane to give a betaine [23, 24, 79], which is subjected to deprotonation to give a β-oxido phosphonium ylide. Trapping with a proton source followed by treatment with a base forms the thermodynamically more stable *trans*-oxaphosphetane, which yields an *E*-alkene via elimination of a phosphine oxide. This reaction relies on the betaine as a readily epimerizing intermediate and generally gives very high *E* selectivity.

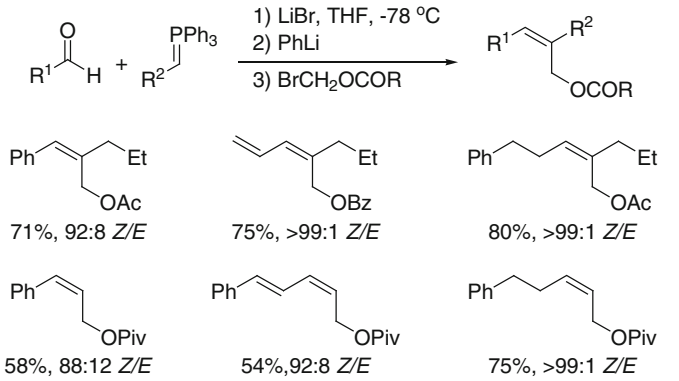


Scheme 13 The Schlosser modification

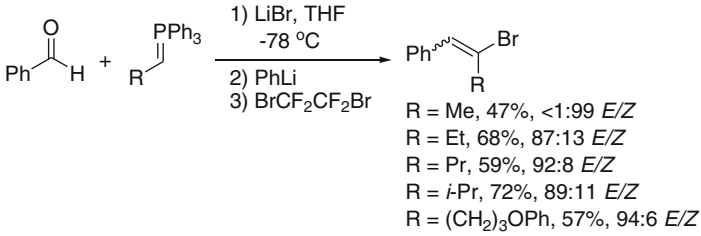


Scheme 14 Stereoselective synthesis of trisubstituted allylic alcohols

Trapping the β-oxido phosphonium ylide intermediate with electrophiles other than a proton constitutes a powerful approach for the stereoselective synthesis of polysubstituted alkenes. Early studies by Corey et al. have shown that aldehydes are able to serve as suitable electrophiles to trap the β-oxido phosphonium ylide intermediate and this reaction provides a highly stereoselective access to trisubstituted allylic alcohols (Scheme 14) [80]. According to Schlosser's modified sequence, a β,β′-dioxido phosphonium ion is expected to be formed by the sequential addition of two aldehydes to the phosphonium ylide. Interestingly, the Wittig elimination from the β,β-dioxido phosphonium ion involves highly selective loss of that oxygen originated in the second aldehyde molecule except in the case of formaldehyde.



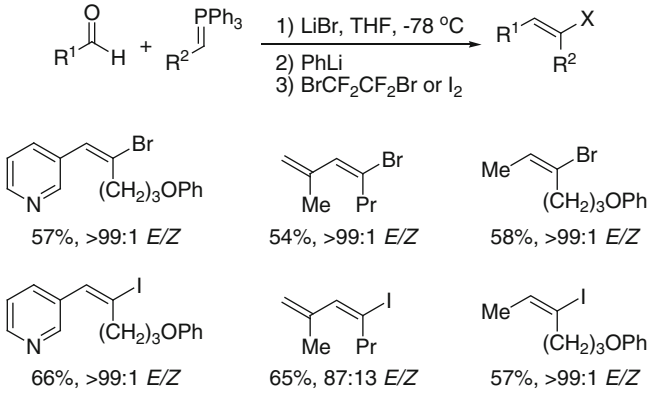
Scheme 15 *Z*-Selective synthesis of di- and trisubstituted allylic esters



Scheme 16 Olefination of alkylidenephosphoranes under Schlosser's conditions

Recently, Hodgson et al. have employed halomethyl esters to trap the β-oxido phosphonium ylide intermediate generated in Schlosser's modified sequence (Scheme 15) [81, 82]. Aromatic, unsaturated, and aliphatic aldehydes serve as suitable substrates for this reaction, which provides a highly *Z*-selective access to di- and trisubstituted allylic esters.

Schlosser's modified sequence is also useful for the preparation of trisubstituted alkenyl halides by trapping the β-oxido phosphonium ylide intermediate with halogen sources such as bromine, $BrCF_2CF_2Br$, and iodine [83, 84]. Studies by Hodgson et al. have shown that the stereochemical outcome is acutely sensitive to the size of the alkylidene group in the original alkylidenetriphenylphosphorane [85]. Although the reaction with ethylidenetriphenylphosphorane gives exclusive *Z* selectivity, the employment of higher alkylidenetriphenylphosphorane leads to good to excellent *E* selectivity (Scheme 16). Under optimized conditions, the reaction of alkylidenetriphenylphosphoranes with aldehydes followed by in situ lithiation and subsequent bromination or iodination provides a highly stereoselective access to *E*-alkenyl bromides and iodides (Scheme 17).



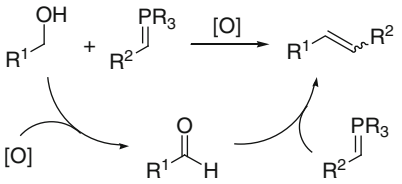
Scheme 17 *E*-Selective synthesis of trisubstituted alkenyl halides

2.4 One-Pot Wittig Reaction

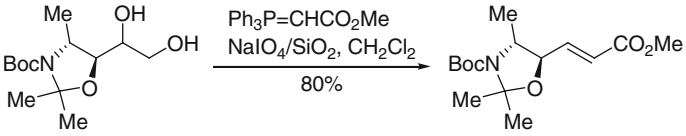
Typically, the Wittig reaction requires complete formation of phosphonium ylides prior to the addition of aldehydes or ketones. If the preparation of the reactants is compatible with the Wittig reaction conditions, the alkene synthesis could be significantly facilitated through a one-pot procedure. Such modifications not only represent greener routes to alkenes through minimizing the amounts of solvents and reagents needed for the reactions and purifications, but also avoid the isolation of sensitive reactants.

2.4.1 Tandem Alcohol Oxidation/Wittig Reaction

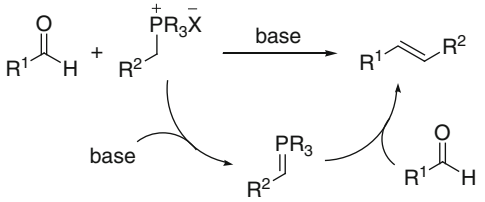
Alcohols often serve as precursors for aldehydes and, moreover, they are more stable, less toxic, and cheaper than the latter. In situ oxidation of alcohols to aldehydes during the Wittig reaction can avoid handling aldehydes, especially when they are volatile, toxic, and/or highly reactive (Scheme 18). The Wittig reaction of stabilized phosphonium ylides is compatible with a number of oxidants such as MnO_2 [86–89], Dess–Martin [90], $BaMnO_4$ [91], *o*-iodoxybenzoic acid (IBX) [92, 93], pyridinium chlorochromate (PCC) [94], and SO_3·Py [95]. In some cases, semistabilized and nonstabilized phosphonium ylides are amenable to the tandem alcohol oxidation/Wittig reaction [88, 89]. Recently, Park et al. have reported an Ru/AlO(OH) catalyzed one-pot synthesis of α,β-unsaturated esters from alcohols and stabilized phosphonium ylides using molecular oxygen as a terminal oxidant [96]. Alonso and Yus et al. have disclosed a nickel nanoparticle promoted one-pot Wittig reaction of primary alcohols with alkylidenetriphenylphosphoranes [97, 98].



Scheme 18 Tandem alcohol oxidation/Wittig reaction



Scheme 19 Tandem glycol oxidative cleavage/Wittig reaction



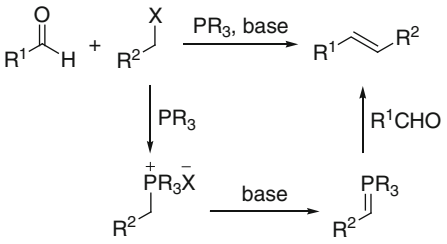
Scheme 20 One-pot Wittig reaction of phosphonium salts

Another approach for the in situ generation of aldehydes in the presence of stabilized phosphonium ylides is the oxidative cleavage of glycols using $NaIO_4$ on silica gel (Scheme 19) [99]. The simultaneous, one-pot oxidative cleavage/Wittig reaction of carbohydrates and amino acid derivatives affords a number of synthetically useful alkenes with high *E* selectivity.

2.4.2 One-Pot Wittig Reaction of Phosphonium Salts

In general, nonstabilized and semistabilized phosphonium ylides are prepared by deprotonation of the corresponding phosphonium salts with strong bases that are incompatible with aldehydes or ketones. However, some studies have shown that these phosphonium ylides can be generated in the presence of aldehydes by treatment of the corresponding phosphonium salts with a weaker base such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) [100], NaOH, LiOH [101, 102], KOH [103], or K_2CO_3 [49, 104, 105] (Scheme 20). In addition, these bases promote the one-pot Wittig reaction of phosphonium salts with aldehydes in a number of solvents such as toluene, tetrahydrofuran, dimethyl sulfoxide, isopropanol, and water.

Scheme 21 One-pot Wittig reaction of alkyl halides

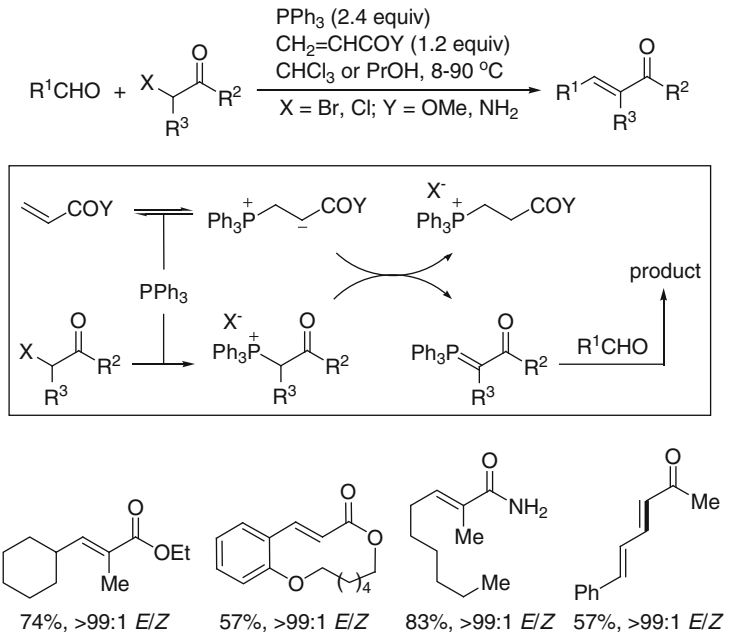


2.4.3 One-Pot Wittig Reaction of Alkyl Halides

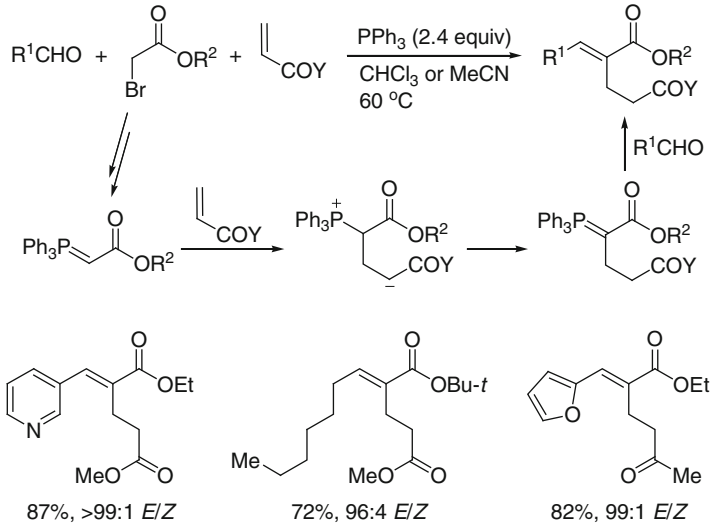
An even more convenient alkene synthesis has been realized through a one-pot Wittig reaction of aldehydes with alkyl halides involving in situ preparation of phosphonium salts and ylides (Scheme 21). This type of one-pot Wittig reaction proceeds in an organic solvent, in water, or without solvent in the presence of triphenylphosphine (or tributylphosphine) and a base such as triethylamine [106], K_2CO_3 [107], $NaHCO_3$ [108], LiOH [109], nanocrystalline MgO [110], or tetrabutylammonium fluoride (TBAF) [111]. Interestingly, zinc powder has also been employed to promote this type of one-pot Wittig reaction [112, 113]. These conditions allow a variety of α-halo carbonyl compounds and benzylic halides to undergo olefination with aldehydes to give conjugated alkenes with high *E* selectivity.

Bases can be generated in situ in a one-pot Wittig reaction of alkyl halides. Studies by Buddrus have shown that ethylene oxide can trap the halide anion of the phosphonium salt, which is formed in situ by the reaction of triphenylphosphine with an alkyl halide, to generate an alkoxide anion as a strong base [114, 115]. Recently, Tian et al. have found that triphenylphosphine in combination with an electron-deficient alkene can mediate the one-pot Wittig reaction of aldehydes with α-halo carbonyl compounds for the synthesis of polysubstituted alkenes in an excellent *E* selective fashion (Scheme 22) [116]. This protocol has been applied to the construction of an α,β-unsaturated macrolide with exclusive *E* selectivity. The key to realizing this one-pot Wittig reaction rests on the ability of the phosphine to undergo a Michael-type addition to the electron-deficient alkene to generate a zwitterion, which serves as an organic base to deprotonate the phosphonium salt formed by the nucleophilic attack of the phosphine on the α-halo carbonyl compound. The resulting phosphonium ylide reacts with the aldehyde to give an alkene. The appropriate choice of the phosphine and the electron-deficient alkene prevents unwanted side reactions such as the Rauhut–Currier and Morita–Baylis–Hillman reactions [117].

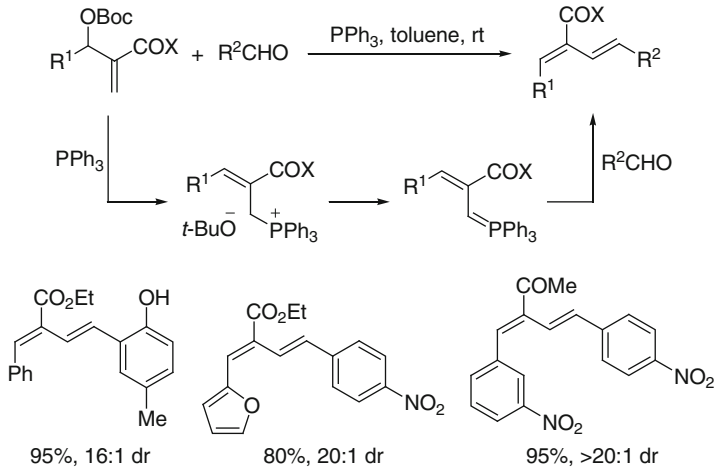
When the addition of the aldehyde is postponed, the in situ generated phosphonium ylide will undergo a Michael addition to the electron-deficient alkene followed by proton transfer to generate another phosphonium ylide (Scheme 23). Based on these transformations, Tian et al. have developed a one-pot, stepwise, three-component reaction of aldehydes, α-haloacetates, and terminal alkenes in the



Scheme 22 Phosphine/alkene-mediated one-pot Wittig reaction



Scheme 23 One-pot, stepwise, three-component reaction of aldehydes, α-haloacetates, and terminal alkenes



Scheme 24 One-pot Wittig reaction of allylic carbonates

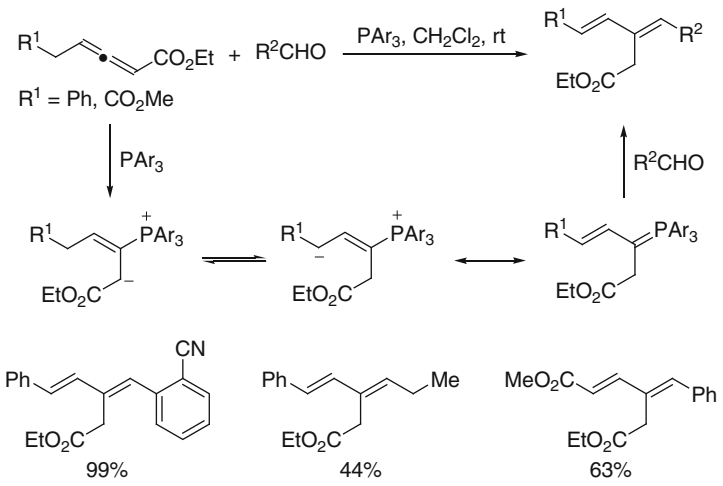
presence of triphenylphosphine to afford a range of trisubstituted alkenes with excellent *E* selectivity [116].

2.4.4 One-Pot Wittig Reaction of Allylic Carbonates

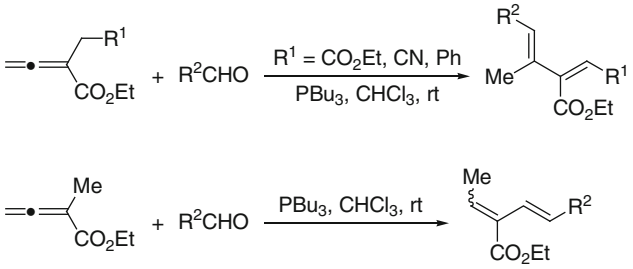
The attack of phosphines on certain carbon electrophiles can generate phosphonium salts along with bases, which are strong enough to deprotonate phosphonium salts to yield phosphonium ylides. In 2010, He et al. reported a one-pot Wittig reaction of aldehydes with allylic carbonates, activated by electron-withdrawing groups, in the presence of a stoichiometric amount of triphenylphosphine at room temperature (Scheme 24) [118]. This protocol provides an access to a variety of 1,2,4-trisubstituted 1,3-dienes with high diastereoselectivity.

2.4.5 One-Pot Wittig Reaction of Allenoates

A few functionalized allylic phosphonium ylides are generated by the nucleophilic attack of phosphines on certain allenoates followed by a set of proton transfers. Taking advantage of this chemistry, He et al. have developed a triarylphosphine mediated olefination of aldehydes with γ-substituted allenoates to afford trisubstituted conjugated dienes in moderate to excellent yields and with high *E* selectivity (Scheme 25) [119]. Similarly, the reaction of aldehydes with α-substituted allenoates has been developed in the presence of tributylphosphine to afford polysubstituted conjugated dienes (Scheme 26) [120, 121].



Scheme 25 One-pot Wittig reaction of γ-substituted allenoates



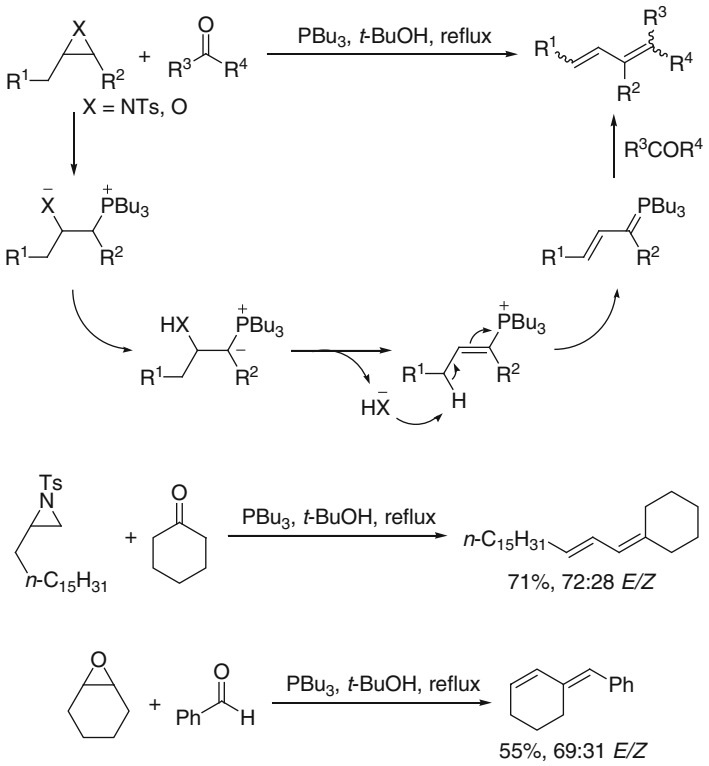
Scheme 26 One-pot Wittig reaction of α-substituted allenoates

2.4.6 One-Pot Wittig Reaction of Aziridines or Epoxides

Allylic phosphonium ylides can also be generated in situ by the nucleophilic attack of phosphines on aziridines (or epoxides) followed by a set of proton transfers. On the basis of these reaction pathways, Hou et al. have realized a slightly *E* selective synthesis of conjugated dienes from aldehydes (or ketones) and aziridines (or epoxides) in the presence of tributylphosphine (Scheme 27) [122].

2.4.7 One-Pot Wittig Reaction of Gramine

Magomedov et al. have developed a highly *E* selective synthesis of 3-vinylindoles by direct coupling of gramine with aldehydes in the presence of tributylphosphine (Scheme 28) [123]. This reaction has been proposed to proceed through elimination



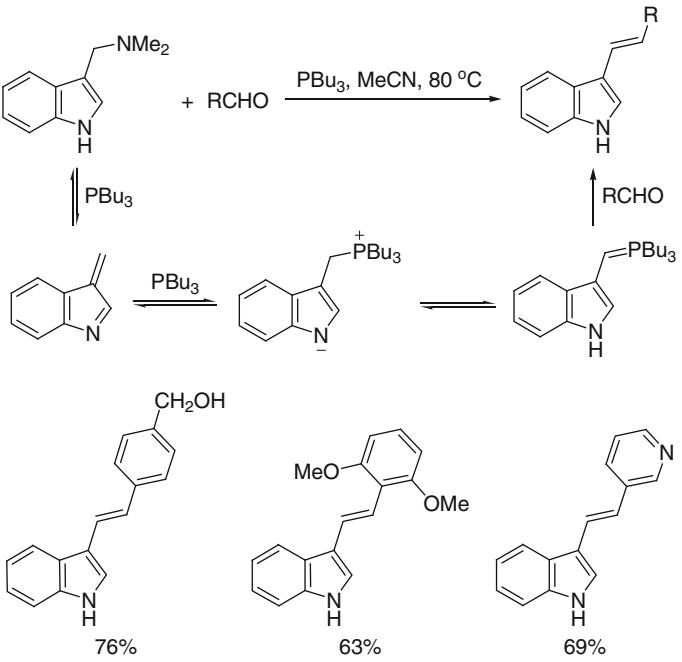
Scheme 27 One-pot Wittig reaction of aziridines or epoxides

of dimethylamine, conjugate addition with tributylphosphine, proton transfer, and the Wittig reaction.

2.4.8 One-Pot Wittig Reaction via Carbene Transfer

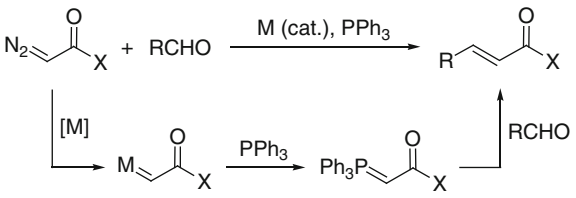
Extensive studies have shown that phosphonium ylides are readily generated in situ from triphenylphosphine and α-diazo carbonyl compounds through carbene transfer in the presence of a catalytic amount of a metal complex derived from Re [124–126], Ru [127–130], Ir [131], Fe [132–137], Cu [138, 139], or Co [140, 141] (Scheme 29). The conditions for carbene transfer are well compatible with aldehydes and ketones, and the metal catalyzed one-pot Wittig reaction of aldehydes (or ketones) with α-diazo carbonyl compounds proceeds smoothly to give electron-deficient alkenes with high *E* selectivity.

Triethyl phosphite has been employed by Carreira et al. in the one-pot Wittig reaction via carbene transfer [142]. Notably, the phosphonium ylides bearing oxygen substituents are not accessible by the standard method of phosphite alkylation due to the Michaelis–Arbuzov reaction [143], and the phosphate byproducts



Scheme 28 One-pot Wittig reaction of gramine

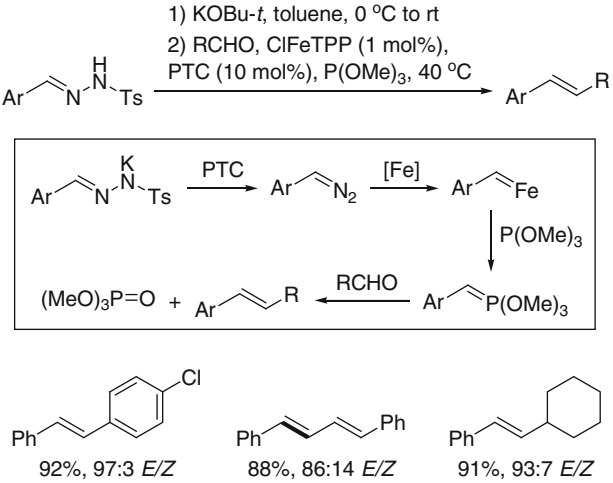
Scheme 29 One-pot Wittig reaction via carbene transfer



are easily removed upon aqueous workup. Aggarwal et al. have found that the reaction of aldehydes with hydrazones (diazo precursors) in the presence of trimethyl phosphite and a catalytic amount of mesotetraphenylporphyrin iron chloride (ClFeTPP) proceeds smoothly to give aryl-substituted alkenes with high *E* selectivity (Scheme 30) [144].

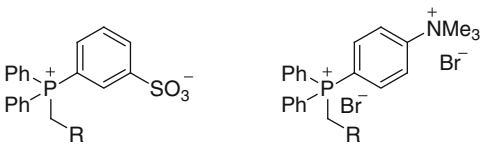
2.5 Removal of Phosphine Oxides

For a typical Wittig reaction, the separation of the alkene product from the phosphine oxide byproduct is carried out by chromatography. To facilitate the

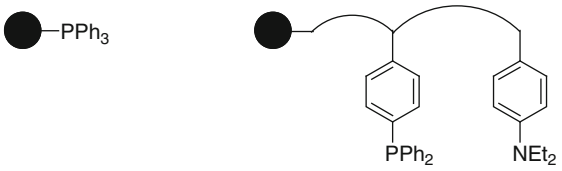


Scheme 30 Olefination of aldehydes with hydrazones via carbene transfer

Scheme 31 Ion-supported phosphonium salts



Scheme 32 Polymer-supported reagents



purification of the alkene product, a few methods have been developed by modifying the *P*-substituent of the phosphonium ylide.

The employment of an ion-supported phosphonium ylide allows the alkene product to be purified by simple filtration of the reaction mixture and subsequent removal of the solvent from the filtrate. In this regard, a sulfonate anion [145] and an ammonium cation [146] have been introduced to the phosphonium salt by Chan and Togo, respectively (Scheme 31). The recovered ion-supported phosphine oxide byproduct is subjected to reduction to regenerate the corresponding phosphine, which can be reused for the Wittig reaction.

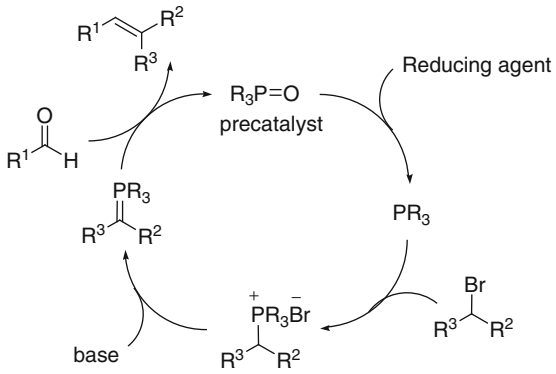
A similar purification method for the alkene product employs a polymer-supported reagent. Westman has developed a one-pot Wittig reaction of alkyl halides with aldehydes mediated by a polymer-supported phosphine and potassium carbonate under microwave irradiation (Scheme 32) [147]. Recently,

Toy et al. have realized this type of one-pot Wittig reaction using a bifunctional polymeric reagent containing the phosphine and amine moieties [148].

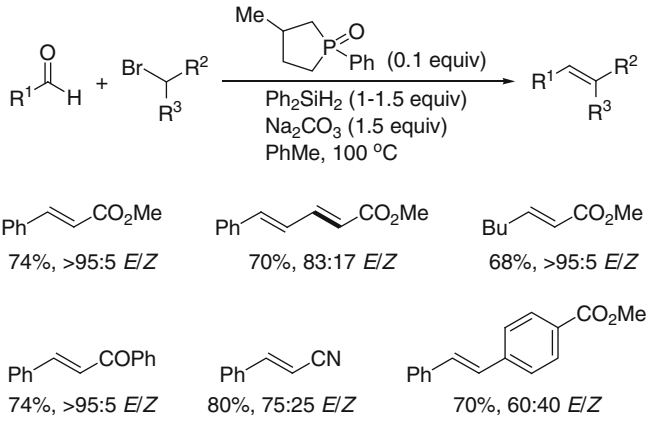
Sinou et al. have developed a Wittig reaction of stabilized perfluorinated phosphonium ylides with aldehydes performed in a perfluorosolvent. This protocol allows an easy separation of the alkene product from the perfluorinated phosphine oxide byproduct by simple liquid-liquid extraction [149].

2.6 *Catalytic Wittig Reaction*

The Wittig reaction is not atom-economic and, moreover, complete removal of the phosphine oxide byproduct is not always straightforward. To address these issues, O'Brien and Chass et al. have recently developed a Wittig reaction catalytic in phosphine. This reaction rests on the chemoselective reduction of the phosphine oxide byproduct with Ph_2SiH_2 and regenerates the phosphine (the active catalyst) without affecting other reaction components (Scheme 33) [150]. In the presence of 10 mol% of the phosphine oxide precatalyst and a stoichiometric amount of Ph_2SiH_2, a variety of aldehydes undergo olefination with α-bromo carbonyl compounds or even benzylic bromides to give the corresponding alkenes in good yields (Scheme 34). Since the structure of the phosphonium ylide has a substantial impact on the stereochemical outcome, further development of the catalytic Wittig reaction will make it possible to control stereoselective alkene synthesis by using a phosphine that is difficult to prepare.



Scheme 33 Proposed mechanism for a catalytic Wittig reaction



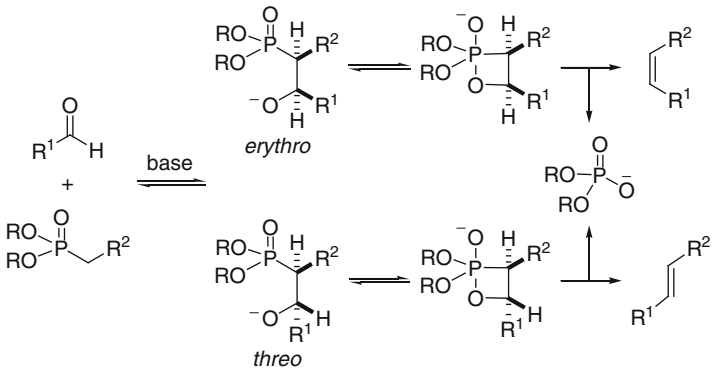
Scheme 34 Catalytic Wittig reaction

3 The Horner–Wadsworth–Emmons Reaction

A very useful modification of the Wittig reaction involves the reaction of phosphonate-stabilized carbanions with aldehydes or ketones, which is known as the Horner–Wadsworth–Emmons (HWE) reaction [7, 151, 152]. This reaction was originally described by Horner et al. [153, 154] and further defined by Wadsworth and Emmons [155]. Phosphonate-stabilized carbanions are more nucleophilic and more basic than phosphonium ylides. They are prepared by the addition of suitable bases to the corresponding alkylphosphonates, which are readily accessible through the Michaelis–Arbuzov reaction of trialkyl phosphites with alkyl halides (usually α-halo carbonyl compounds) [143]. In contrast to the Wittig reaction, the HWE reaction yields phosphate salt byproducts that are water-soluble and hence are readily separated from the desired alkene products by simple extraction.

3.1 Mechanism

The mechanism of the HWE reaction is closely related to that of the Wittig reaction. It is generally accepted that the addition of the phosphonate-stabilized carbanion to the aldehyde gives a mixture of *erythro* and *threo* isomeric β-oxido phosphonates under reversible conditions (Scheme 35) [156–160]. The *erythro* and *threo* intermediates cyclize to form *cis*- and *trans*-oxaphosphetanes, rapid elimination of which affords *Z*- and *E*-alkenes, respectively. It should be pointed out that the decomposition of the β-oxido phosphonate intermediate requires an electron-withdrawing group (e.g., ester, acyl, amide, cyano, sulfonyl, vinyl, or aryl) α to the phosphonate moiety. Otherwise, the final product is a β-hydroxy phosphonate

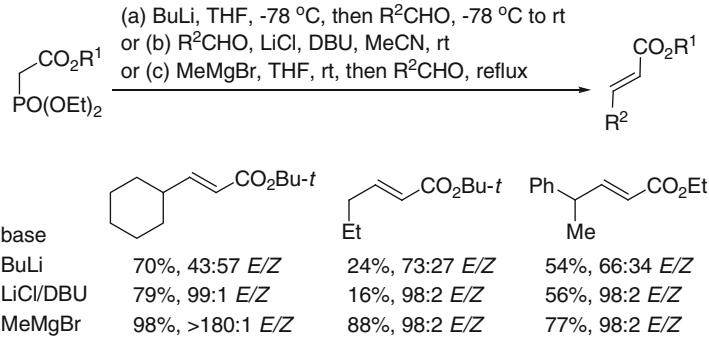


Scheme 35 Mechanism of the HWE reaction

after hydrolysis of the reaction mixture [161, 162]. The stereochemical outcome of the HWE reaction is a result of both kinetic and thermodynamic controls upon the reversible formation of *erythro* and *threo* aldehyde/phosphonate adducts and their decomposition to alkenes.

3.2 Scope and Limitations

The HWE reaction has become one of most versatile tools for the synthesis of conjugated alkenes, and its stereoselectivity primarily depends on the nature of the phosphonate. In general, the HWE reaction of simple dialkyl alkylphosphonates gives preferentially *E*-alkenes, and in many cases the *E* selectivity can be further enhanced by employing bulkier *P*-substituents [163]. Moreover, the stereoselectivity of the HWE reaction is more or less affected by a few other variables such as the base used for the formation of the phosphonate-stabilized carbanion, ion, solvent, and temperature [164, 165]. Alkali metal bases such as BuLi, NaH, and KHMDS are commonly employed for the generation of reactive phosphonate-stabilized carbanions, and in many cases the nature of the metal counterion of the base can significantly affect the stereoselectivity. Sano and Nagao et al. have found that the use of *i*-PrMgBr as the base leads to better stereoselectivity than that of BuLi in the HWE reaction of aldehydes with 2-fluoro-2-diethylphosphonoacetic acid for the synthesis of (*Z*)-α-fluoro-α,β-unsaturated carboxylic acids [166]. Recently, MeMgBr has been identified by Davies et al. as an effective base for a highly *E* selective HWE reaction (Scheme 36) [167]. When compared to commonly used bases such as BuLi and LiCl/DBU (see below), MeMgBr promotes the HWE reaction to give α,β-unsaturated esters in much higher yields and with equal or superior *E* selectivity.



Scheme 36 HWE reaction promoted by different bases

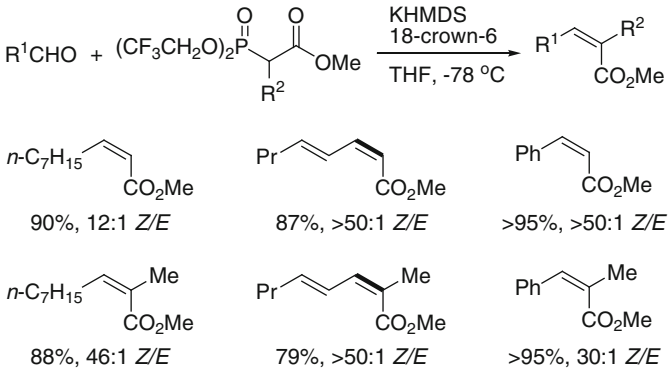
Weaker bases have been employed to reduce or even avoid the epimerization of the stereocenter adjacent to the aldehyde group of the substrate in the HWE reaction. For example, Myers et al. have found that lithium 1,1,1,3,3,3-hexafluoroisopropoxide (LiHFI) promotes the HWE olefination of epimerizable aldehydes with dimethylphosphonoacetates to afford the desired alkenes with little or no epimerization and with high *E* selectivity [168].

Tertiary amines, such as TBD, DBU, and *N*-ethylpiperidine, can serve as alternatives to strong ionic bases in the HWE reaction [100]. In addition, the HWE reaction can proceed smoothly in the presence of DBU under neat conditions [169, 170]. Recently, Verkade et al. have employed $P[N(i\text{-Bu})CH_2CH_2]_3N$ to promote the HWE reaction at room temperature for the synthesis of α,β-unsaturated esters, ketones, nitriles, and fluorides [171]. In these cases, phosphonate-stabilized carbanions are generated in situ in the presence of aldehydes.

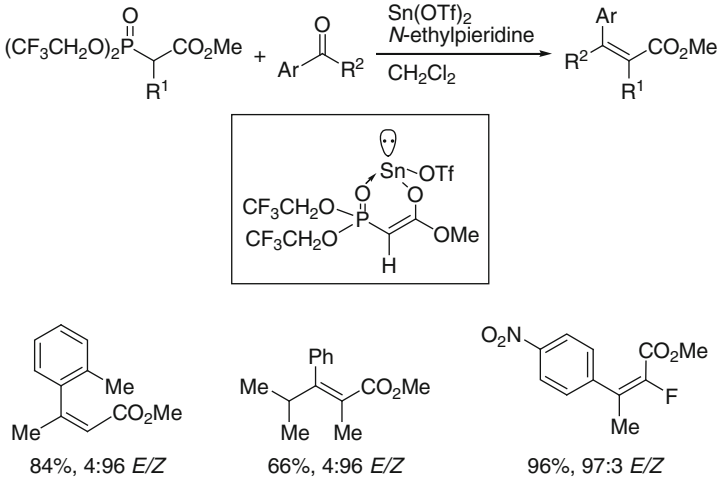
Bases in combination with Lewis acids are powerful in promoting the HWE reaction with many substrates that are incompatible with strong bases. In 1984, Masamune and Roush et al. reported mild conditions using lithium chloride and DBU (or $i\text{-Pr}_2NEt$) [172], and later Rathke et al. extended this Lewis acid/base system to lithium or magnesium halides with triethylamine [173]. Recently, Helquist et al. have employed $Zn(OTf)_2$, TMEDA, and DBU to promote the HWE reaction of aldehydes with diethylphosphonoacetic acid to give α,β-unsaturated carboxylic acids with excellent *E* selectivity [174].

3.3 The Still Modification

It is a useful strategy to achieve *Z* selectivity in the HWE reaction by tuning the electronic and steric properties of the *P*-substituents of phosphonate-stabilized carbanions. In 1983, Still et al. described the employment of bis(2,2,2-trifluoroethyl)phosphonoacetates in the HWE reaction (Scheme 37) [175]. This modification, together with strongly dissociating conditions (KHMDS and



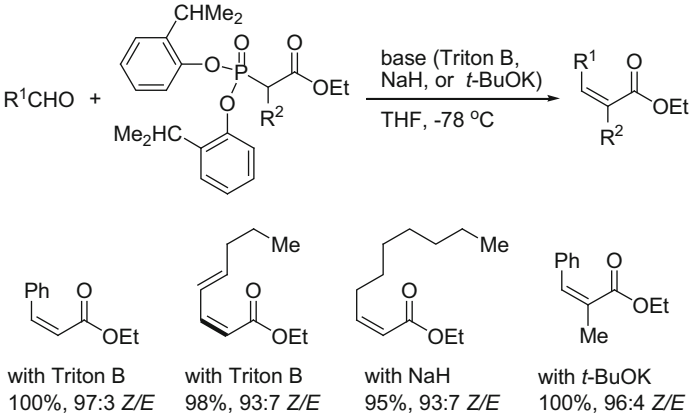
Scheme 37 The Still modification



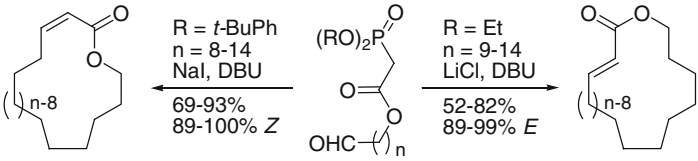
Scheme 38 Olefination of aromatic ketones with bis(2,2,2-trifluoroethyl)phosphonoacetates

18-crown-6 in tetrahydrofuran), allows the synthesis of a variety of di-and tri-substituted α,β-unsaturated esters with high *Z* selectivity. Recently, Touchard has found that in the Still modification 18-crown-6 can be replaced with TDA-1 [N$(CH_2CH_2OCH_2CH_2OMe)_3$], a cheap and readily available K^+ chelating agent [176].

Nagao et al. have employed $Sn(OTf)_2$ and *N*-ethylpiperidine to extend the Still modification to the olefination of aromatic ketones, and a range of tri- and tetrasubstituted α,β-unsaturated esters have been prepared with high stereoselectivity (Scheme 38) [177–180]. In all cases, the aromatic and ester moieties are located on the same side of the double bond of the alkene product. The role of $Sn(OTf)_2$ in enhancing the stereoselectivity is related to its ability to chelate with the phosphonate-stabilized enolate to form a six-membered nucleophilic species.



Scheme 39 The Ando modification

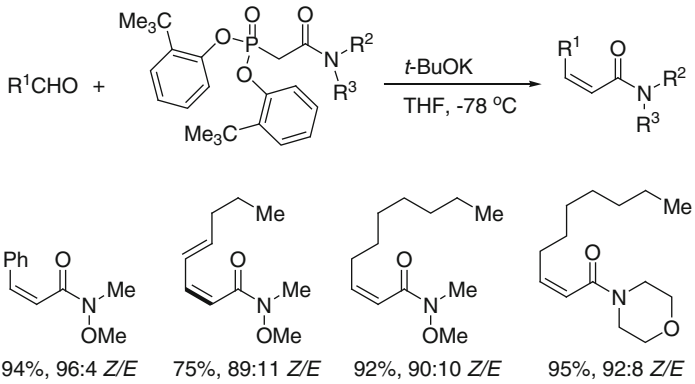


Scheme 40 Intramolecular HWE reaction

Although this reaction can be accelerated by microwave irradiation, it gives much lower *Z* selectivity [181].

3.4 The Ando Modification

In 1995, Ando reported that α,β-unsaturated esters could be obtained with high *Z* selectivity from the HWE reaction of aldehydes with diphenylphosphonoacetates in the presence of benzyltrimethylammonium hydroxide (Triton B) or NaH in tetrahydrofuran [182]. Later, Ando [183–186], Motoyoshiya [187, 188], and Touchard [189, 190] further defined this protocol by modifying diphenylphosphonoacetates and found that the employment of bis(*o*-alkylphenyl)phosphonoacetates led to higher *Z* selectivity (Scheme 39). The combination of NaH and NaI has been identified as an effective base/additive system to improve the *Z* selectivity [191]. Moreover, the Ando modification has recently been applied to the ring closure of various macrolides with high *Z* selectivity, which is complementary to that of traditional intramolecular HWE reaction (Scheme 40) [192, 193].



Scheme 41 Synthesis of (*Z*)-α,β-unsaturated amides

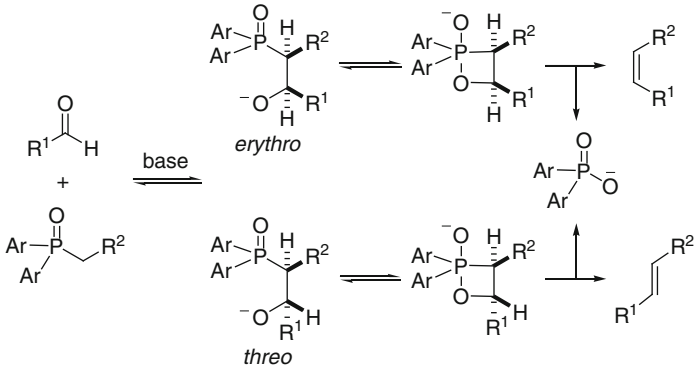
In addition, the Ando modification has been extended to the preparation of α,β-unsaturated amides with high *Z* selectivity from the corresponding aldehydes and diarylphosphonoacetamides (Scheme 41) [194, 195].

4 The Horner–Wittig Reaction

The olefination reaction of phosphine oxide-stabilized carbanions with aldehydes or ketones is referred to as the Horner–Wittig reaction [5, 7, 196]. This reaction was originally described by Horner et al. [153, 154]. Phosphine oxides bearing *P*-alkyl groups can be prepared by hydrolysis of phosphonium salts, by the reaction of organometallic reagents with halophosphines followed by oxidation, or by the reaction of organometallics with phosphinyl halides. Phosphinate salts are generated as byproducts in the Horner–Wittig reaction, and they are water-soluble and are readily removed from the desired alkene products by simple extraction.

4.1 Mechanism

The mechanism of the Horner–Wittig reaction is similar to that of the HWE reaction. The addition of the phosphine oxide-stabilized carbanion to the aldehyde gives a mixture of *erythro* and *threo* isomeric β-oxido phosphine oxides under reversible conditions (Scheme 42). When a nonlithium base is used and the negative charge is stabilized by the R^2 group, the *erythro* and *threo* intermediates cyclize to form *cis*- and *trans*-oxaphosphetanes that decompose to give *Z*- and *E*-alkenes, respectively. The *E*-alkene product is formed preferentially because elimination of the *trans*-oxaphosphetane occurs much faster than that of the *cis*- one.



Scheme 42 Mechanism of the Horner–Wittig reaction

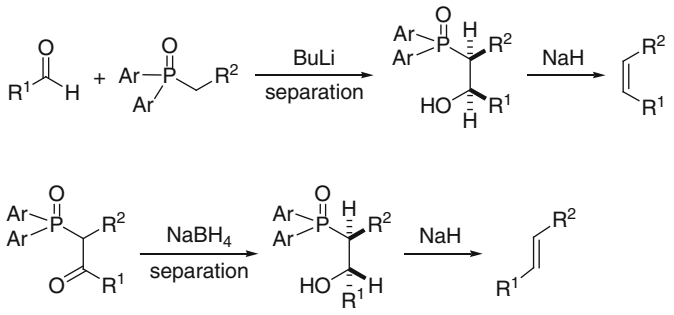
When the reaction is carried out at low temperature in the presence of a lithium base, β-hydroxy phosphine oxides can be isolated but in general with unsatisfied diastereoselectivity. Upon treatment with a nonlithium base such as NaH, KOH, or KOBu-*t*, β-hydroxy phosphine oxides are ready to undergo stereospecific *syn*-elimination to afford the corresponding alkenes.

4.2 Scope and Limitations

A variety of functionalized alkenes has been directly obtained with *E* selectivity from the Horner–Wittig reaction of aldehydes (or ketones) with phosphine oxide-stabilized carbanions bearing in the α position certain functional groups such as aryl [197], vinyl [198–200], cyano [201], sulfonyl [202], isoxazole [203], amino [204], or alkylthio [205]. The functional group provides stabilization for the negative charge of the β-oxido phosphine oxide intermediate and lowers the activation energy for the elimination step to form an alkene (Scheme 42).

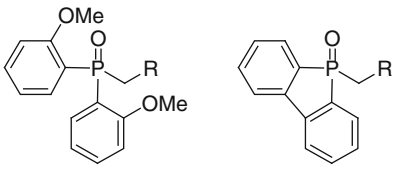
The unique feature of the Horner–Wittig reaction is that the phosphine oxide-stabilized carbanion/aldehyde addition intermediates, β-hydroxy phosphine oxides, can be isolated and purified, and the elimination step is stereospecific for the formation of the corresponding alkenes. Usually the reaction gives predominantly *erythro* adducts that can be converted to *Z*-alkenes upon being treated with bases (Scheme 43). However, *threo* β-hydroxy phosphine oxides can be obtained by reduction of the corresponding β-keto phosphine oxides, which are prepared by oxidation of β-hydroxy phosphine oxides, or by acylation of lithio phosphine oxides with esters [206].

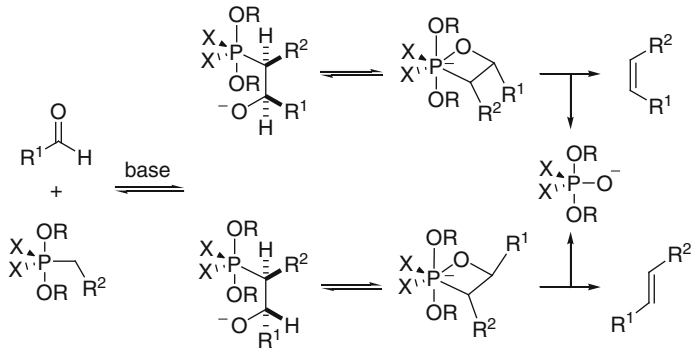
While diphenylphosphine oxide has been employed most frequently to activate the carbon nucleophiles in the Horner–Wittig reaction, alternative use of bis(*o*-anisyl) phosphine oxide [207] or dibenzylphosphole oxide [208–210] leads to better stereoselectivity for alkene synthesis (Scheme 44).



Scheme 43 Stepwise Horner–Wittig reaction

Scheme 44 Bis(*o*-anisyl) phosphine oxides and dibenzylphosphole oxides

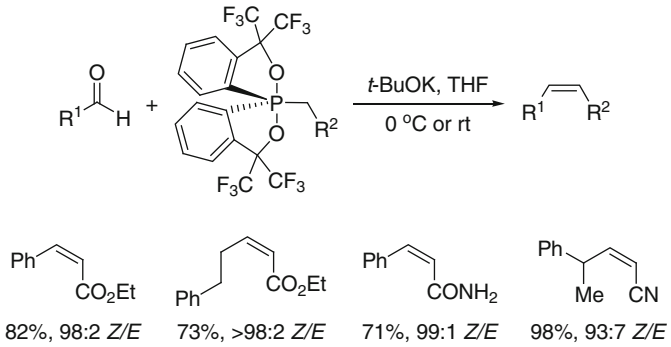




Scheme 45 Mechanism of the Evans–Akiba reaction

5 The Evans–Akiba Reaction

Evans [211] and Akiba [212] reported in 1996 and 1997, respectively, that some pentacoordinated phosphorane-stabilized carbanions could undergo olefination with aldehydes, which we suggest be called the Evans–Akiba reaction. Similar to the HWE and Horner–Wittig reactions, this reaction has been proposed by Akiba et al. to proceed through diastereoselective carbonyl addition, cyclization, and elimination to yield an alkene (Scheme 45) [213–216]. It is noteworthy that the phosphorus atom is hexacoordinated in the four-center transition state.



Scheme 46 Olefination of pentacoordinated spirophosphoranes

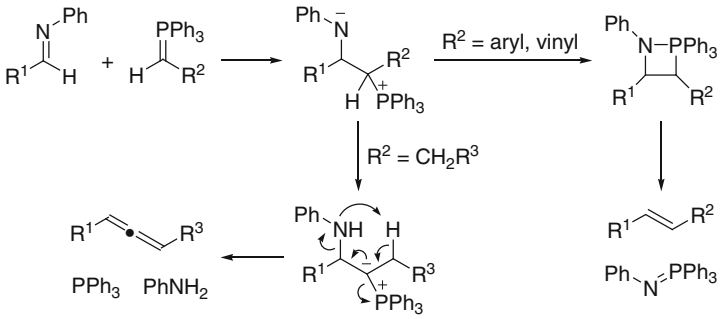
A variety of pentacoordinated spirophosphoranes undergo olefination with aldehydes in the presence of *t*-BuOK to give α,β-unsaturated esters, amides, and nitriles with high *Z* selectivity (Scheme 46) [212, 217]. This method has recently been extended to the *Z* selective olefination of ketones by modifying the pentacoordinated spirophosphoranes, which are readily prepared through the reaction of the corresponding P-H phosphoranes with α-halo carbonyl compounds in the presence of DBU [218].

6 Olefination of Imines with Phosphonium Ylides

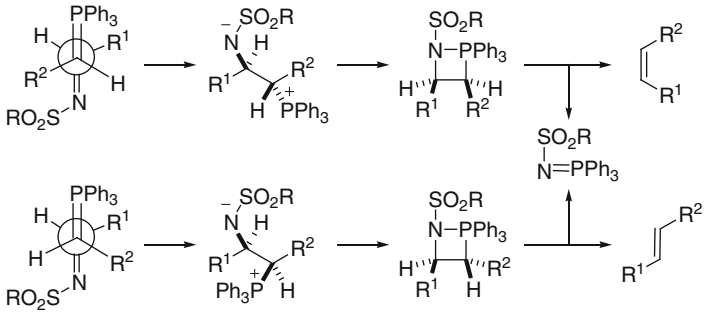
In 1963, Bestmann et al. disclosed that treatment of *N*-benzylideneaniline with semistabilized triphenylphosphonium ylides at 150–180 °C afforded alkenes, but with nonstabilized triphenylphosphonium ylides at 130–150 °C afforded allenes [219, 220]. For a long time this protocol had not been improved and developed into a useful stereoselective alkene synthesis, probably owing to the high reaction temperature and inconvenient operation. Recently, Tian et al. have developed a highly tunable stereoselective olefination reaction of imines with triphenylphosphonium ylides at low temperature by employing sulfonyl groups to activate the imines [221–223].

6.1 Mechanism

Bestmann has proposed a mechanism involving initial formation of a betaine intermediate through the addition of the phosphonium ylide to the *N*-phenyl imine (Scheme 47) [224]. The betaine intermediate is isolable and decomposes at high temperature. In the reaction with the semistabilized phosphonium ylide, the betaine intermediate cyclizes to form an azaphosphetane that eliminates an



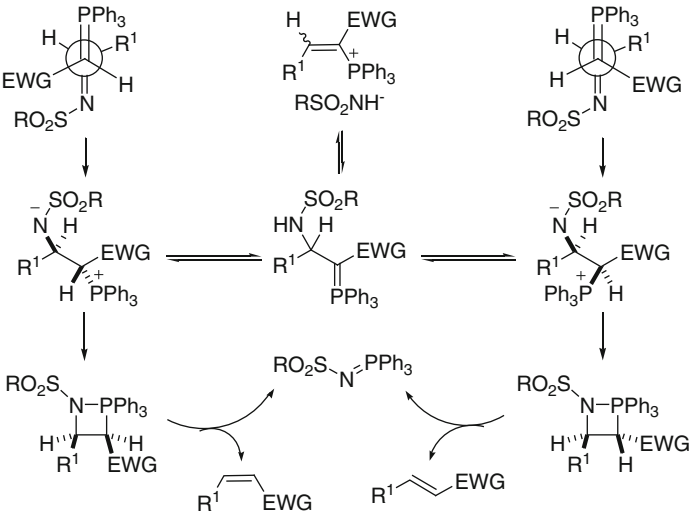
Scheme 47 Proposed mechanisms for the reactions of *N*-phenyl imines with phosphonium ylides



Scheme 48 Proposed mechanism for the olefination of *N*-sulfonyl imines with nonstabilized phosphonium ylides

iminophosphorane to yield an alkene. However, in the reaction with the nonstabilized phosphonium ylide, the betaine intermediate undergoes proton transfer followed by fragmentation to release an allene, a phosphine, and an arylamine.

Tian et al. have found that the betaine intermediate generated from an *N*-sulfonyl imine and a nonstabilized phosphonium ylide decomposes smoothly at room temperature according to ^{31}P NMR spectroscopic analysis [222]. Moreover, the HBr salt of the betaine has been isolated after treatment of the reaction mixture with HBr at low temperature, and converts to the alkene product with the same *Z*/*E* ratio as that of the corresponding olefination reaction. These results suggest that the stereoselectivity for alkene synthesis originates from the diastereoselective addition of the nonstabilized phosphonium ylide to the *N*-sulfonyl imine, wherein the stereoselectivity is finely tuned by the interactions among the *N*-sulfonyl, R^1, R^2, and Ph_3P groups that develop as the ylide and the imine approach one another (Scheme 48). If the R^2 group suffers greater steric repulsion from the R^1 group than that from the *N*-sulfonyl group, an *anti*-betaine intermediate is generated preferentially and decomposes to give a *Z*-alkene via a *cis*-azaphosphetane intermediate. Otherwise, an *E*-alkene is produced preferentially.

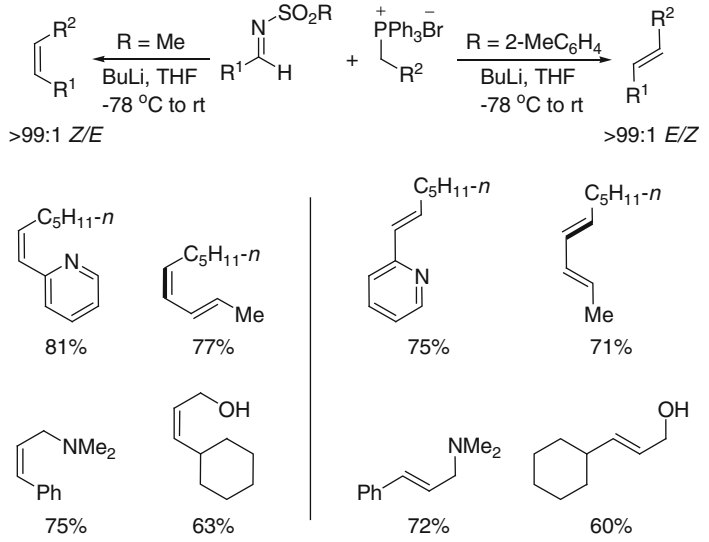


Scheme 49 Proposed mechanism for the olefination of *N*-sulfonyl imines with stabilized phosphonium ylides (*EWG* electron-withdrawing group)

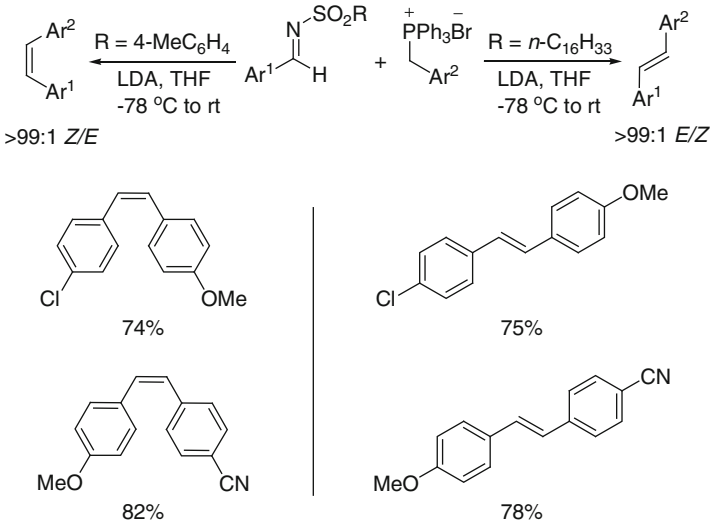
For the reaction with a stabilized phosphonium ylide, the betaine intermediate undergoes proton transfer and even extrudes a sulfonamide group to give a vinyl phosphonium salt that can be trapped with water, a stabilized phosphonium ylide [223], or nitromethane (solvent) [225]. These findings suggest that the conversion of the betaine to the azaphosphetane is much slower than the interconversion between the two betaine diastereomers (Scheme 49). Thus, the *Z*/*E* ratio for the alkene product does not correspond to the diastereoselectivity for the initial imine/ylide addition. Instead, the *Z*/*E* selectivity is decided by the different rates for the transformation of the two betaine diastereomers into their corresponding azaphosphetanes.

6.2 Scope and Limitations

The stereoselectivity for the olefination of *N*-sulfonyl imines with phosphonium ylides is significantly affected by the substituent on the imine nitrogen atoms and the bases used for ylide formation. Studies by Tian et al. have shown that BuLi is the base of choice for the reaction with nonstabilized triphenylphosphonium ylides [222]. A range of *N*-methanesulfonyl imines undergo olefination with alkylidenetriphenylphosphoranes to afford *Z*-alkenes in good yields and with greater than 99:1 stereoselectivity (Scheme 50). The corresponding *E*-alkenes have been obtained with the same level of stereoselectivity by employing an *o*-toluenesulfonyl group to activate imines. In addition, this protocol provides a convenient access to both *Z*- and *E*-allylic alcohols and amines with extremely high stereoselectivity.

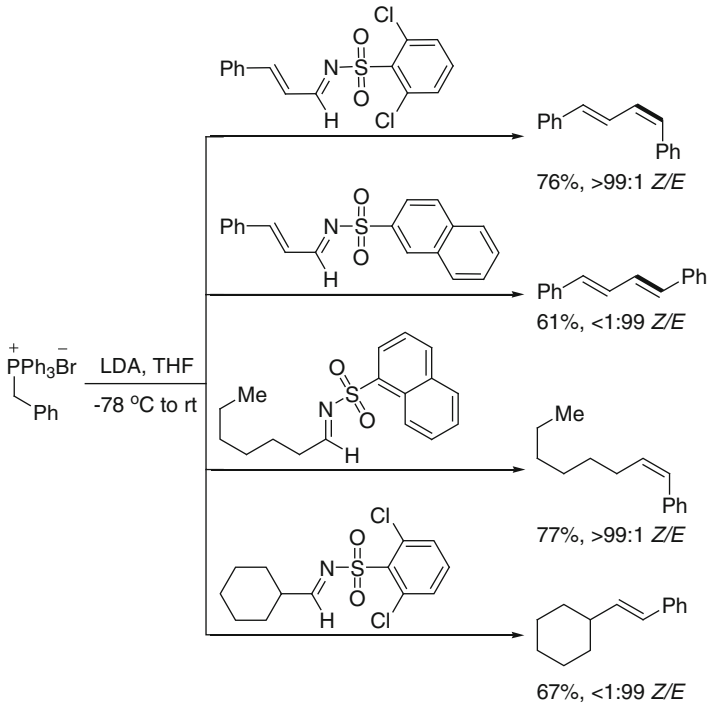


Scheme 50 Olefination of *N*-sulfonyl imines with nonstabilized triphenylphosphonium ylides



Scheme 51 Olefination of *N*-sulfonyl aromatic imines with benzylidenetriphenylphosphoranes

LDA has been identified as the base of choice for the olefination of *N*-sulfonyl imines with semistabilized triphenylphosphonium ylides [221]. A range of *N*-(*p*-toluenesulfonyl) aromatic imines undergo olefination with benzylidenetriphenylphosphoranes to give *Z*-stilbene derivatives with greater than 99:1 stereoselectivity (Scheme 51). The exclusive *Z* selective olefination reaction

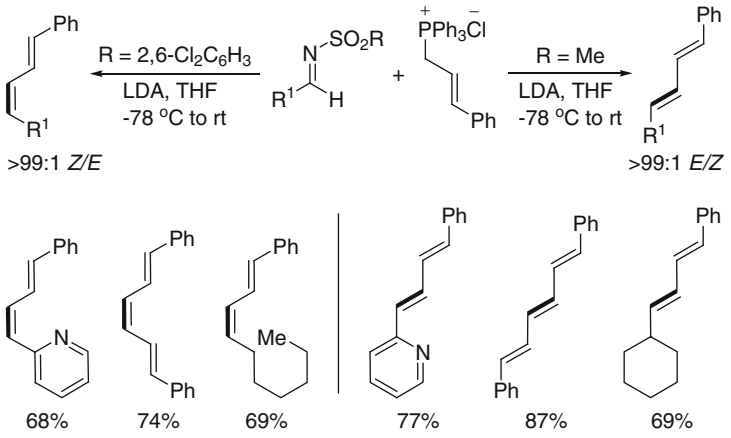


Scheme 52 Olefination of *N*-sulfonyl α,β-unsaturated and aliphatic imines with benzylidenetriphenylphosphoranes

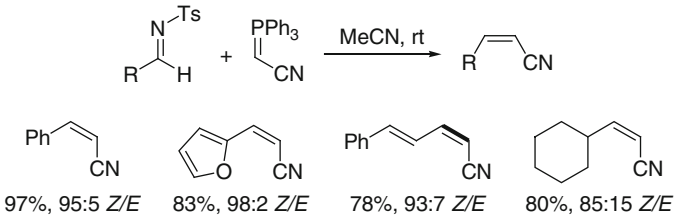
has been extended to α,β-unsaturated and aliphatic imines activated by a 2,6-dichlorobenzenesulfonyl group and a 1-naphthenesulfonyl group, respectively (Scheme 52). Moreover, an *n*-hexadecanesulfonyl group, a 2-naphthenesulfonyl group, and a 2,6-dichlorobenzenesulfonyl group are able to activate aromatic, α,β-unsaturated, and aliphatic imines to yield conjugated *E*-alkenes with greater than 99:1 stereoselectivity, respectively.

The olefination reaction of *N*-sulfonyl imines with allylidenetriphenylphosphoranes gives extremely high stereoselectivity with regard to the newly formed carbon-carbon double bonds when appropriate sulfonyl groups are employed (Scheme 53) [221]. While the reaction with *N*-methanesulfonyl imines gives exclusive *E* selectivity, the use of a 2,6-dichlorobenzenesulfonyl group to activate imines results in exclusive *Z* selectivity.

In 2005, Abdou et al. reported that the reaction of *N*-aryl imines with stabilized phosphonium ylides in chloroform under reflux gave α,β-unsaturated nitriles, esters, and ketones with exclusive *E* selectivity but in only about 20% yield [226]. Recently, Tian et al. have found that the employment of *N*-(*p*-toluenesulfonyl) imines to react with (cyanomethylene)triphenylphosphorane in



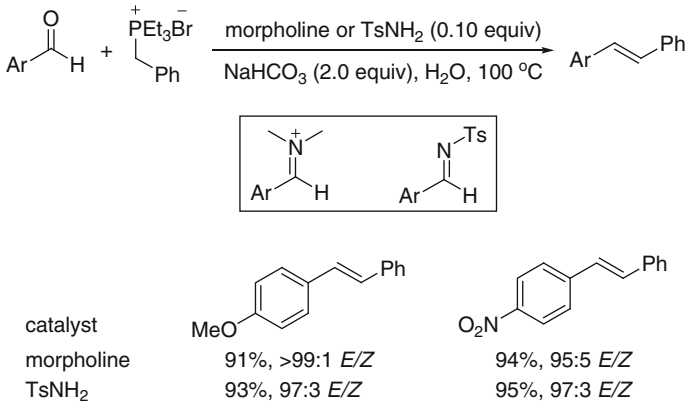
Scheme 53 Olefination of *N*-sulfonyl imines with allylidenetriphenylphosphoranes



Scheme 54 Olefination of *N*-sulfonyl imines with (cyanomethylene)triphenylphosphorane

acetonitrile at room temperature leads to the formation of α,β-unsaturated nitriles in good to excellent yields and *Z* selectivity (Scheme 54) [223]. In contrast, elevated temperature is needed for the olefination reaction of *N*-sulfonyl imines with ester-, amide-, and ketone-stabilized phosphonium ylides, which gives α,β-unsaturated esters, amides, and ketones with high *E* selectivity, respectively.

A related example disclosed recently by McNulty et al. is a one-pot Wittig reaction of aldehydes with phosphonium salts in the presence of 10 mol% of morpholine, L-proline or *p*-toluenesulfonamide and 2.0 equiv. of $NaHCO_3$ (Scheme 55) [227]. This reaction gives high *E* selectivity. A rapid and reversible condensation of the aldehyde with the amine (derivative) catalyst has been proposed to form an iminium or an imine intermediate that is subjected to olefination with the in situ generated phosphonium ylides, though a base-catalyzed pathway is not ruled out. It has been confirmed that an *N*-sulfonyl imine can be formed quantitatively from the corresponding aldehyde and sulfonamide under the reaction conditions.



Scheme 55 Amine- or sulfonamide-catalyzed one-pot Wittig reaction

7 Conclusion

During the last five decades, phosphonium-, phosphonate-, phosphine oxide-, and pentacoordinated phosphorane-stabilized carbanions have been identified as effective nucleophiles for the stereoselective olefination of aldehydes and ketones. Modifying the structures of these nucleophiles along with optimizing reaction conditions results in the formation of a wide variety of polysubstituted alkenes in a highly stereoselective manner. Recently, replacement of aldehydes with the corresponding *N*-sulfonyl imines in the Wittig reaction has further improved the stereoselectivity for the synthesis of 1,2-disubstituted alkenes by tuning the electronic and steric properties of the substituents on the imine nitrogen atoms.

A number of methods have been developed for the in situ preparation of either aldehydes or phosphonium ylides during the Wittig reaction. These one-pot procedures significantly shorten the synthetic sequences for alkenes synthesis, and represent greener routes through minimizing the amounts of solvents and reagents needed for the reactions and purifications. To improve the atom-economy, a Wittig reaction catalytic in phosphine has recently been developed.

In contrast to many other methods commonly employed for stereoselective alkene synthesis such as elimination, alkenylation, alkene metathesis, alkyne addition, the Julia olefination, and the Peterson olefination [1–3], the olefination reactions of phosphorus-stabilized carbon nucleophiles remain very powerful for modern stereoselective alkene synthesis owing to their convenience, complete positional selectivity, and generally high levels of geometrical control. However, further modifications of these olefination reactions are definitely needed to broaden substrate scope, enhance stereoselectivity, and improve environmental impacts.

Acknowledgments We are grateful for the financial support from the National Natural Science Foundation of China (21172206, 20972147, and 20732006) and the National Basic Research Program of China (973 Program 2010CB833300).

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Top Curr Chem (2012) 327: 239–270
DOI: 10.1007/128_2012_322

Published online: 1 May 2012

Alkene Synthesis Through Transition Metal-Catalyzed Cross-Coupling of *N*-Tosylhydrazones

Yan Zhang and Jianbo Wang

Abstract In this chapter, alkene synthesis based on the reaction of *N*-tosylhydrazones is described. The reactivity of tosylhydrazones is determined by either the acidity of α-proton and hydrazone proton or the electropositivity of the carbon of C=N bond. This leads to diverse reactivities and a series of *N*-tosylhydrazone-based olefination methodologies. Both non-catalytic and transition metal-catalyzed olefinations from *N*-tosylhydrazones are introduced in this chapter. Most of the transition metal-catalyzed reactions proceed via metal carbene transformations. The synthesis of alkenes through Pd-catalyzed cross-coupling reactions of *N*-tosylhydrazones is particularly attractive and will be discussed in detail.

Keywords Alkene synthesis · Cross-coupling · Metal carbene · *N*-Tosylhydrazones

Contents

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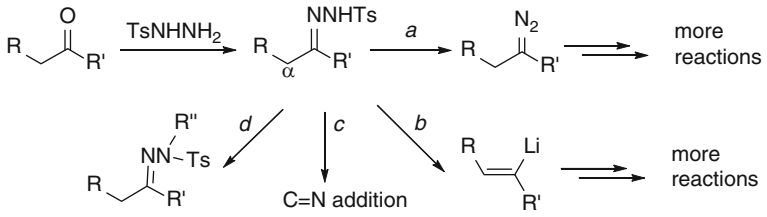
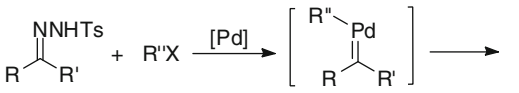


Fig. 1 The reaction of tosylhydrazones

1 Introduction

N-Tosylhydrazones are common substrates in organic chemistry and are readily prepared by condensation of carbonyl compounds with *N*-tosylhydrazide. As stable and readily available reagents, tosylhydrazones (*N*-tosylhydrazones) have been widely applied in organic synthesis over the decades. The reactivity of tosylhydrazone is determined by acidic protons on α-position of hydrazone, N–H proton, or the electropositive carbon of C=N bond. Generally, the N–H proton of tosylhydrazone is easily removed by base to generate a diazo intermediate (Fig. 1, pathway *a*) [1, 2]. However, the acidic α-proton of tosylhydrazone can be abstracted by a strong base, such as organolithiums, to form vinyl lithium (Fig. 1, pathway *b*) [2]. These intermediates are very important in organic synthesis. The carbon of the tosylhydrazone C=N bond is electropositive and thus can be attacked by nucleophiles (Fig. 1, pathway *c*) [3]. Finally, the N–H bond of tosylhydrazones can be substituted (Fig. 1, pathway *d*) [4, 5]. Therefore tosylhydrazones can undergo various reactions and thus have been important substrates for current organic synthesis.

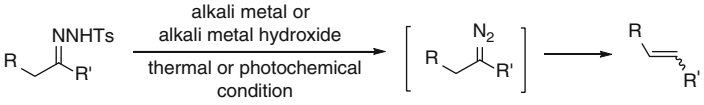
The construction of C=C bonds is fundamental in organic chemistry. Up to now, several olefination methods by direct use of carbonyl compounds have been established. The Wittig reaction is one of the most preeminent reactions which can provide a general way to perform olefination of aldehydes/ketones. Since the discovery of the Wittig reaction, some modified versions with high stereoselectivity have been developed and extended. As derivatives of carbonyl compounds, tosylhydrazones have been involved in various olefination reactions in recent years. Some of the methodologies have an advantage over those using carbonyl compounds directly. In particular, Pd-catalyzed cross-coupling of *N*-tosylhydrazones with a number of reagents involving palladium carbenes have attracted great interest – see (1). Based on these novel catalytic transformations, various functionalized alkenes can be prepared with high stereoselectivity and regioselectivity.



(1)

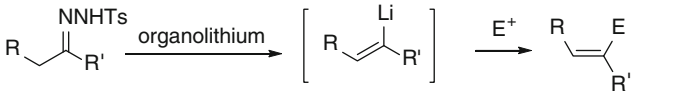
2 Alkene Formation Through Non-catalytic Reactions of *N*-Tosylhydrazones

Pioneering work by Bamford and coworkers demonstrated the alkene synthesis by treatment of *N*-tosylhydrazones derived from ketone with base, the so-called Bamford–Stevens reaction – see (2) [1]. A diazo intermediate is supposed to be initially generated during the process. Subsequent singlet carbene formation in aprotic solvent leads to the *Z*-alkenes predominantly through 1,2-H shift to the carbenic center (Fig. 1, pathway *a*). However, a carbenium ion intermediate is produced in protic solvent and finally affords a mixture of *Z*- and *E*-olefins. Notably, the regioselectivity and stereoselectivity of Bamford–Stevens reaction are also influenced by the non-migrating (i.e., the bystander group) substituents and various stereochemical features of the substrates [6–10].



(2)

The Shapiro reaction is another widely known transformation for alkene synthesis from *N*-tosylhydrazones – see (3) [2]. In this method, strong bases such as organolithium are generally utilized to abstract both hydrazone proton and the less acidic α-proton, leading to the formation of a diazonium group (Fig. 1, pathway *b*). The resulting vinyllithium then reacts readily with different electrophiles (H_2O, alkyl halides, aldehyde, etc.) to afford substituted alkenes [11–15]. The reaction can be considered as a variation of the Bamford–Stevens reaction. However, this method does not lead to high stereoselectivity between the *E* and *Z* isomers of the products. To the best of our knowledge, tosylhydrazones derived from aldehydes are not applicable to the Shapiro reaction because addition of the organolithium to the carbon of the C=N double bond will occur exclusively [16, 17].



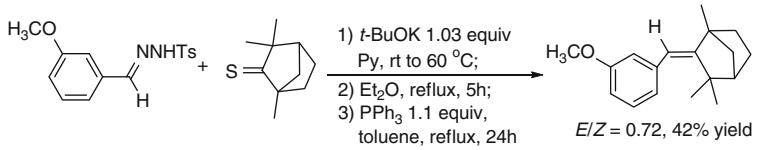
(3)

E = H_2O, alkyl halide, aldehyde and etc

Borane-mediated reduction of α,β-unsaturated tosylhydrazones is another reliable reaction to synthesize alkenes. In this type of reaction, new C=C bonds are formed by an "alkene walk" within the substrates through intramolecular rearrangement [18–21].

Known as Barton–Kellogg olefination, C=C bond formation by the reaction of a thioketone and a ketone through a diazo intermediate has been pioneered by Staudinger's group and further developed by the groups of Barton and Kellogg [22–24]. The thioketone required for the reaction is commonly derived from a

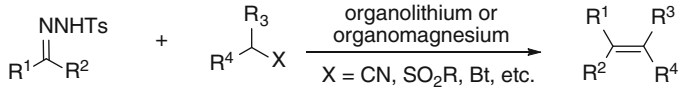
ketone and Lawesson's reagents, and the diazo compounds can be directly utilized or freshly prepared through a one-pot oxidation of hydrazones [25–30]. A recent application of ketone tosylhydrazone for Barton–Kellogg olefination has been reported by Baader and coworkers, but the *E*/*Z* selectivity is low – see (4) [31].



(4)

In 1979, Vedejs and coworkers reported that alkenes were afforded by the reaction of sterically unhindered aldehyde tosylhydrazones with stabilized carbanions through a condensation–fragmentation process [3]. An unusual stereoselectivity for *trans*-alkenes was observed by treating tosylhydrazone of benzaldehyde with butyronitrile – see (5) – R^3 = Et, R^4 = H, X = CN in the presence of lithium diisopropylamide (LDA). Furthermore, Katrizky and coworkers have achieved highly stereoselective synthesis of *E*-stilbene by reaction of tosylhydrazones with benzotriazole-stabilized carbanion with the aid of organolithium [32, 33] – see (5) – X = 1-benzotriazolyl (Bt). This method can be compared with Julia-type olefination, in which aldehyde is the substrate in the place of tosylhydrazone.

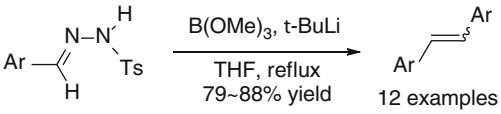
Wicha and coworkers further reported similar reaction of ketone tosylhydrazones by using organomagnesium – see (5) – X = SO_2R [34]. Experimental results showed that the substituents on α and β positions of metal sulfones affected the stereoselectivity of target alkenes. The reaction of lithiated sulfones and β-branched magnesio sulfones generally leads to high *E*-selectivity, albeit the yield is lower. Moreover, the regioselective olefination of the corresponding aldehyde tosylhydrazone containing a potential leaving group such as an alkoxy group or an amino group on the α-position was reported by Chandrasekhar and Wicha, respectively – see (5) – X = SO_2Ar [35–40]. The competing Shapiro reaction could be restrained by employing organomagnesium sulfones instead of lithium reagents [40].



(5)

As mentioned above, the diazo intermediate is initially generated in the Bamford–Stevens process. The diazo carbon will undergo homocoupling if the in situ generated diazo intermediates are consumed too slowly by the reaction partners. However, this coupling is generally inefficient no matter whether the tosylhydrazones salts are treated under thermal or photolytic promotion [41, 42]. In most of the reactions of tosylhydrazones, homocoupling products are detected as by-products because low concentration of diazo compounds is generated in situ under the condition. However, the side reaction may turn into a major one and thus become synthetically useful. In 2001, Kabalka and coworkers investigated the formation of stilbene derivatives with high *trans*-selectivity in good yield through

homocoupling of aryl aldehyde tosylhydrazones in the presence of trialkyl borate and base – see (6) [43]. A stoichiometric quantity of trimethyl borate was required to prevent the possible attack of in situ generated lithium tosylate on the carbene intermediate [44].

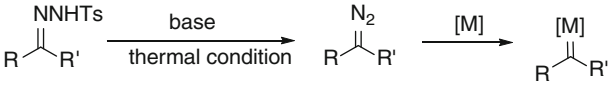


(6)

3 Alkene Formation Through Transition Metal-Catalyzed Reactions of *N*-Tosylhydrazones

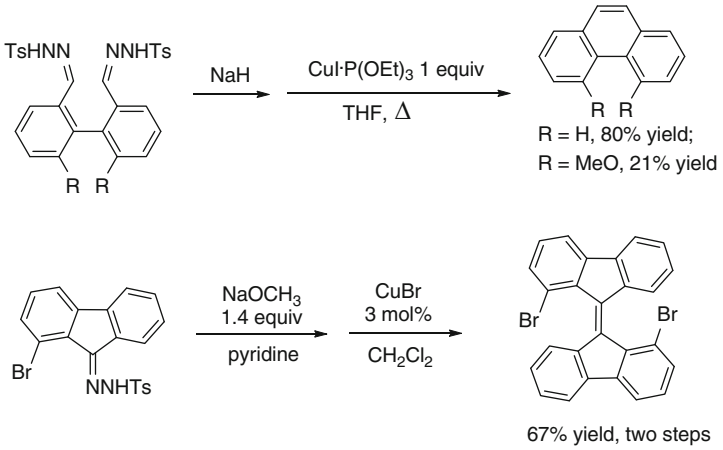
3.1 Introduction

Diazo compounds can be dediazonized by transition metal complexes to generate metallocarbenes, which are important intermediates in various transformations [45–48]. Since tosylhydrazones have been found to be readily available precursors of diazo compounds through the Bamford–Stevens reaction, a series of transition metal-catalyzed reactions of aldehyde tosylhydrazone salts in the presence of base and phase transfer catalyst (PTC) have been reported since 2000 [49–53]. It has been considered that metal carbenes generated from the in situ generated diazo compounds are involved in the catalytic cycle of these reactions – see (7).



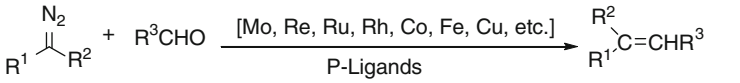
(7)

Alkene formation through homocoupling or 1,2-shift of diazo compounds is a very common process for metal carbene intermediates [54, 55]. These reactions can be used for alkene synthesis from tosylhydrazones. In this context, Jung and co-workers investigated the Cu-promoted intramolecular coupling of bis (tosylhydrazone) in 1991 [41]. Addition of catalytic amounts of CuBr has been found to increase the yield of phenanthrene products – see (8). Scott and coworkers reported another Cu-catalyzed olefination through an efficient one-pot dimerization of tosylhydrazones – see (9) [56]. Low yields of olefin products through Cu- or Rh-catalyzed dimerization of tosylhydrazones have also been reported by Doyle's group [53]. However, the dimerization of tosylhydrazones is reported as undesired side-products in most of the transition metal-catalyzed reactions. Their potential in organic synthesis has not been explored.



3.2 *Wittig-Type Reaction*

With the advancement of catalytic transformation, it was of great interest to find practically useful catalytic olefination in Wittig-type reactions. Catalytic olefination of diazo compounds could be achieved by using transition metal catalysts as reported by Schwartz et al. [57]. A series of catalytic olefination reactions have been developed by treating diazo compounds with aldehydes in the presence of phosphine reagents and metal complexes of Mo, Re, Ru, Rh, Co, Fe, or Cu under mild conditions – see (10) [58–65]. Different pathways involving metalloazines, phosphazines, phosphorus ylides, or metal carbene intermediates have been proposed based on the experimental or computational results. In these reactions the key role of metal carbene intermediates and phosphorus ylides have been confirmed for Fe, Ru, Co, and Re-catalyzed procedures [62–65]. These reactions can be considered as organometallic variation of Wittig reactions.



Aggarwal and coworkers have reported that *E*-olefins can be obtained with high selectivity by the reaction of aldehyde tosylhydrazones with aldehydes catalyzed by an iron complex (*meso*tetraphenylporphyrin iron chloride, ClFeTPP) in the presence of $(MeO)_3P$. $BnEt_3Cl$ is utilized as PTC (Fig. 2) [66, 67]. The reaction mechanism is proposed to be a Wittig-type reaction by ^{31}P NMR measurement. Phosphorus ylides are assumed to be generated through metal carbene transfer to phosphate. The ratio of *E/Z* olefins has been achieved up to 98:2 with high yields. Furthermore, the potassium salts of hydrazones are found to be more suitable for the reaction. Besides, changing of substituents on phosphorus from carbon to oxygen led to better *E* selectivity. The efficiency of this reaction has been demonstrated by the highly stereoselective synthesis of trans-stilbene derivative, which a potential anticancer compound [66, 67].

Zhu and coworkers have reported an alternative preparation of *trans* alkenes through an Rh(II)-catalyzed reaction of aldehydes with pentafluorobenzaldehyde

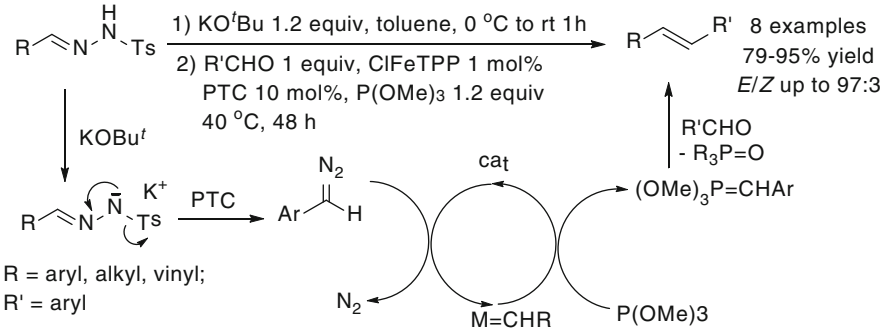
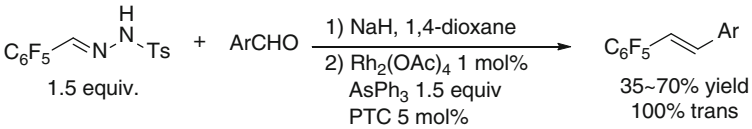


Fig. 2 Synthesis of disubstituted alkenes by Fe-catalyzed reaction of tosylhydrazones with aldehydes

tosylhydrazones in the presence of triphenyl arsine – see (11) [68]. During the reaction, arsonium ylide is assumed to be generated in situ through similar carbene transfer with subsequent Wittig-type reaction.



(11)

Compared with the typical Wittig reaction, the Wittig-type reaction under catalytic conditions provides a way to couple aldehydes with tosylhydrazones for the preparation of substituted stilbenes with good *trans*-selectivity. The method also avoids the separate preparation of phosphorus ylide. Thus, this method provides an alternative pathway of C=C bond formation and extends the scope of substrates from alkyl halides to various aldehydes. However, more than 1 equiv. of phosphorus reagent is still needed. This method has not been well applied to ketone olefination.

3.3 Pd-Catalyzed Cross Coupling Reactions

Palladium complexes have been widely utilized as catalysts in various coupling reactions for the construction of C–C and C–X bonds [69–71]. Although not as common as Rh(II) and Cu(I) catalysts, Pd complexes have also been used as catalysts in the reaction with diazo compounds. Over the last few decades, some Pd-catalyzed reactions of diazo compounds, such as cyclopropanations and polymerizations, have been reported [72]. In 2001, Van Vranken and coworkers reported the first Pd-catalyzed coupling reaction of diazo compounds with benzyl halides (Fig. 3) [73]. Through the reaction of trimethylsilyl diazomethane and benzyl halides, C=C bonds can be constructed and substituted styrenes are obtained in good yield.

The reaction was suggested to be initiated by oxidative addition of benzyl halides to Pd(0) complex. The generated Pd(II) complex then decomposes diazo

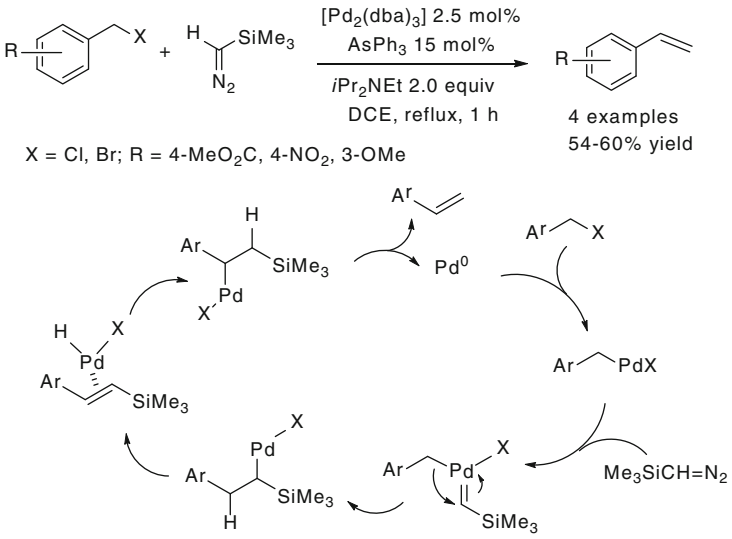


Fig. 3 Pd-catalyzed cross-coupling of trimethylsilyldiazomethane with benzyl halides

compound to produce Pd carbene intermediate. Subsequent carbene migratory insertion into the palladium–carbon σ bond was assumed to be the key step in the procedure (Fig. 3) [73–76]. Although mechanistically interesting, this reaction hasn't attracted much attention until very recently. In the past few years, this type of cross-coupling reaction has been revisited and a series of Pd-catalyzed coupling reactions of diazo compounds have been developed by the groups of Van Vranken, Yu, Wang and coworkers [72, 77–86]. Various substituted alkenes can be accessed through these reactions. However, the studies on the unstable diazo compounds without an electron-withdrawing group in the α-position are limited because of their inconvenient preparation and handling of diazo substituents. To overcome such difficulty, the in situ generation of diazo compounds is expected to play the role. The studies in the past decades have demonstrated that tosylhydrazones can be used as precursors for diazo substrates in transition metal-catalyzed reactions [67, 75, 76]. In this section, recent progress on alkene preparation from palladium-catalyzed reaction of tosylhydrazones will be discussed in detail. These reactions are classified through different palladium carbene migratory insertion processes.

3.3.1 Carbene Insertion into the Palladium–Aryl Bond

Cross Coupling with Aryl Halides

Barluenga and coworkers first employed tosylhydrazones for Pd-catalyzed coupling reaction of aryl halides in the presence of bases (Fig. 4) [87]. The reaction is catalyzed by $Pd_2(dba)_3$ with Xphos as ligand. The tosylhydrazones can be those derived from cyclic ketones, aryl ketones, or alky carboxyaldehydes. Aryl chlorides or bromides

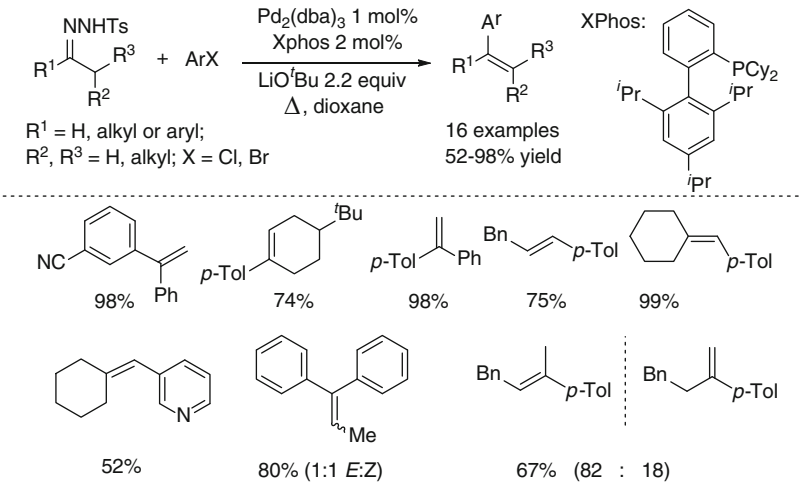
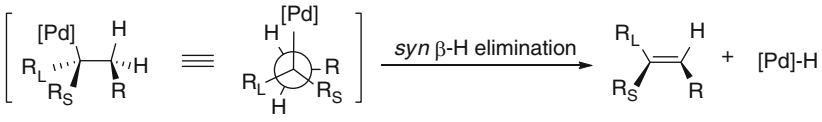


Fig. 4 Synthesis of alkenes through Pd-catalyzed coupling of tosylhydrazones with aryl halides

can undergo the transformation smoothly under the optimized reaction condition. Electron-withdrawing or -donating groups on the aromatic ring of aryl halides are all compatible in the reactions. Thus, the coupling reaction provides a convenient method to synthesize di/tri-substituted olefins from tosylhydrazones.

Similar to the Pd-catalyzed reaction of diazo compounds with benzyl halides [73], the reaction was proposed to be initiated by oxidative addition of aryl halide to Pd(0) species to form aryl palladium(II) complex **A**. Then Pd carbene **B** is produced by decomposition of the in situ generated diazo compound from *N*-tosylhydrazone through Bamford–Stevens reaction with the aid of base under heating. Migratory insertion of Pd carbene to Pd–aryl bond leads to Pd(II) intermediate **C**. The compound then undergoes β-hydride elimination to yield complex **D** with the formation of di- or trisubstituted olefins (Fig. 5).

With this coupling reaction, excellent *trans*-selectivity could be obtained in the preparation of disubstituted alkenes. In the case of trisubstituted olefins, the mixture of *E*/*Z* isomers was commonly isolated with much higher ratios of *E* olefins. The stereoselectivity can be interpreted as follows – see (12). The configuration of final olefin is determined by the *syn* β-hydride elimination in the transition state. The R group is favorable to eclipse with the smaller substituent (Rs) of the vicinal carbon atom to minimize the steric interactions. Thus *trans*-alkenes or trisubstituted *E*-olefins were formed selectively.



(12)

Applying this method, Alami and coworkers prepared a series of 1,1-diarylethylenes containing polyoxygen substituents on the aromatic ring (Fig. 6)

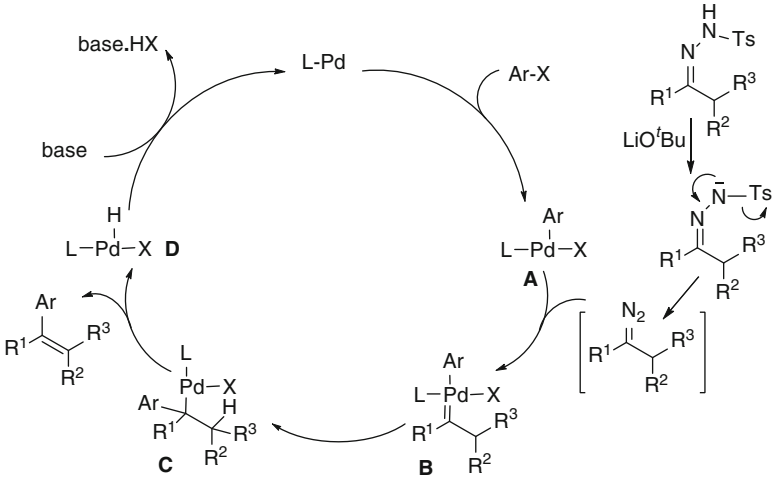


Fig. 5 Mechanism of Pd-catalyzed cross coupling

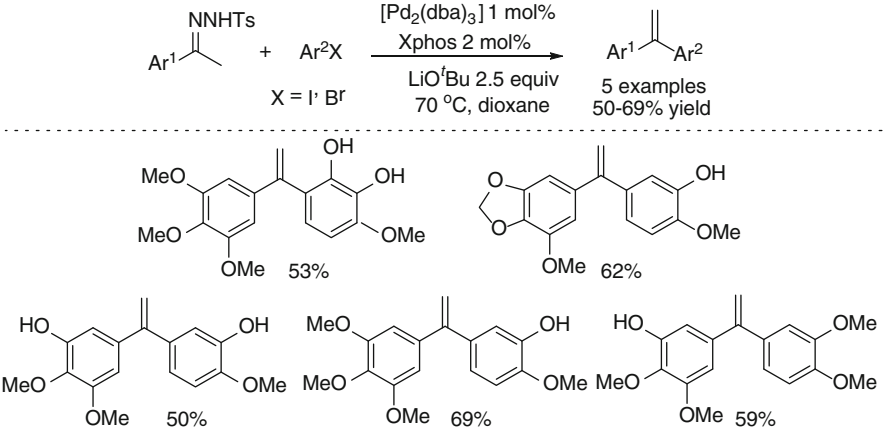


Fig. 6 Synthesis of *iso*CA

[88]. The reactions under the conditions ($Pd_2(dba)_3$-Xphos-LiO^tBu), as developed by Barluenga's group, proceed well to afford the olefins in good yields [87]. The olefin products obtained are isomers of natural *Z*-combretastatins (*iso*CA), a novel class of potent antitubulin agents.

Based on the results of coupling reaction of tosylhydrazones and aryl halides, Barluenga et al. further achieved a one-pot process directly from linear or cyclic carbonyl compounds in the presence of 1.1 equiv. of tosylhydrazide with catalyst $Pd_2(dba)_3$-Xphos (Fig. 7) [89]. In this reaction, tosylhydrazone is produced in situ and subjected to the subsequent reaction without separation. Compared with the reaction starting from pre-formed tosylhydrazones, the scope of ketone substrates and stereoselectivity of products do not exhibit any obvious difference. Moreover,

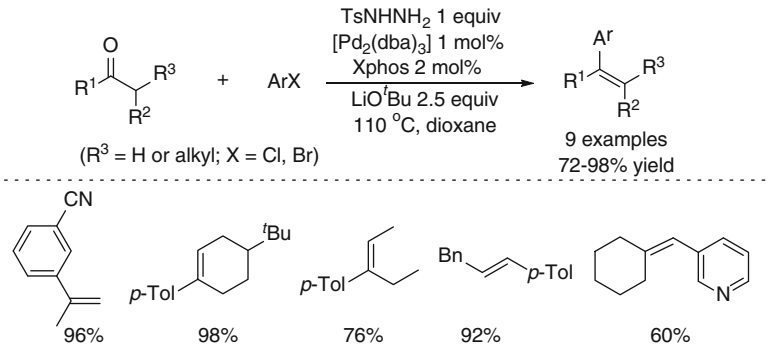


Fig. 7 Synthesis of alkenes by one-pot reaction of carbonyl compounds and aryl halides

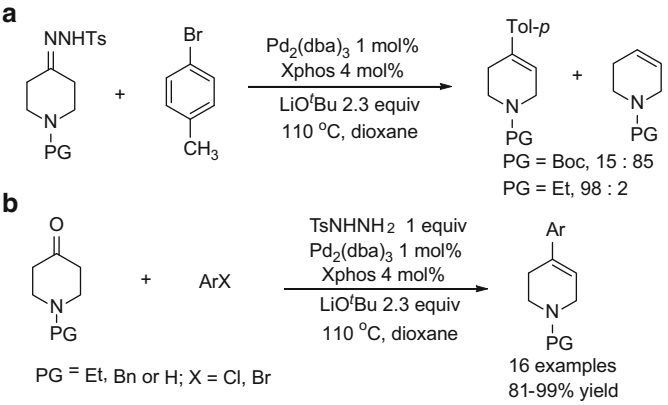


Fig. 8 Synthesis of alkenes through coupling of heterocyclic tosylhydrazones with aryl halides. (**a**) reaction from hydrazone; (**b**) reaction from ketone

the reactions proceed well even in solvent grade dioxane in open air. Experimental results show that the H_2O in situ generated in the first step may be advantageous to the reaction. Interestingly, the reaction of aldehydes also led to good results. No aldol reaction of linear aldehydes was observed and *trans*-olefins were isolated in the reactions exclusively.

In 2008, Barluenga's group further employed the tosylhydrazones from saturated heterocyclic carbonyl compounds for the Pd-catalyzed cross-coupling reaction with aryl halides [89]. In the presence of LiO^{t}Bu, the reaction of *N*-ethyl protected 4-piperidone tosylhydrazone and *p*-bromotoluene was assayed with catalytic system $Pd_2(dba)_3$-Xphos. The reaction shows interesting chemoselectivity depending upon the electronic property of *N*-protected group (N-PG). Electron-withdrawing groups, such as *tert*-butyloxycarbonyl (Boc), led mainly to thermal degradation of tosylhydrazone. However, *N*-ethyl protected tosylhydrazone resulted in the expected coupling reaction with *p*-bromotoluene (Fig. 8a). A similar reaction system has been successfully extended to the coupling of aryl halides with

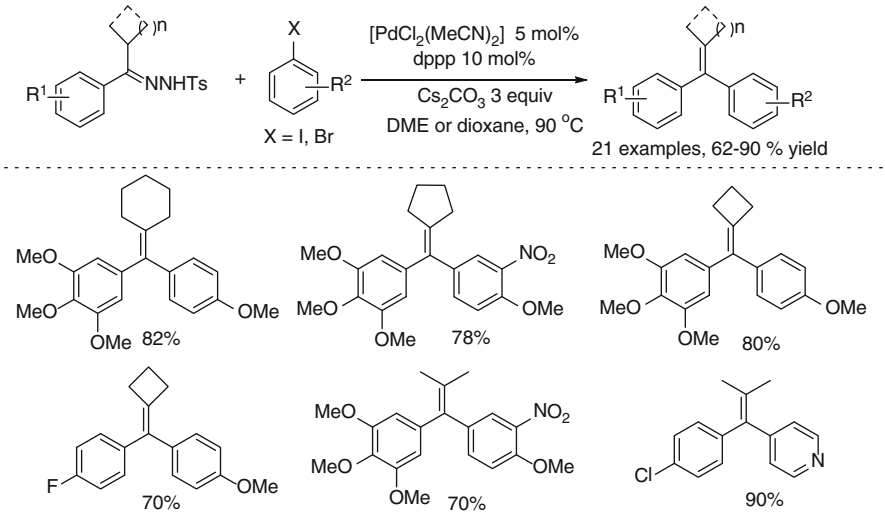
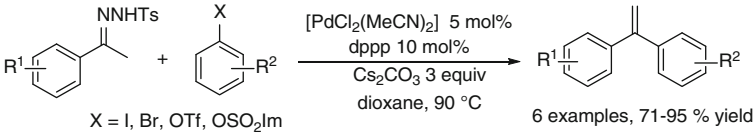


Fig. 9 Synthesis of 1,1-diarylcycloalkylidenes by coupling of sterically hindered tosylhydrazones with aryl halides

corresponding 4-piperidones. Heterocyclic olefins can be obtained in good yields no matter whether the nitrogen atom is unprotected or protected by ethyl and benzyl groups (Fig. 8b).

Previous work has indicated the possibility of cross-coupling reaction of aryl bromide with sterically hindered tosylhydrazones [87, 89]. Alami and coworkers have reported the $PdCl_2(MeCN)_2$-catalyzed reaction of aryl halides with a series of sterically hindered tosylhydrazones containing bulky groups in the α-position. Less sterically demanding phosphine ligand 1,3-bis(diphenylphosphino)propane (dppp) and less basic Cs_2CO_3 were utilized in this reaction (Fig. 9) [90]. Notably, fluoride and chloride substituents on aromatic rings remain intact after the reaction and various 1,1-diarylalkylidenes can be prepared with good yields.

In addition, the optimized reaction conditions ($PdCl_2(MeCN)_2$-dppp-Cs_2CO_3) have been further applied for the coupling of less hindered tosylhydrazones with aryl halides or pseudohalides – see (13). Six 1,1-diarylethylenes with polyoxygen substituents on the aromatic rings were prepared. More reactions of tosylhydrazone with pseudohalides will be introduced later.



(13)

Pd-catalyzed coupling reaction of diazoesters with aryl halides has been proven to be an efficient approach for the preparation of 2-arylacrylates by Wang and coworkers [86]. Accordingly, the Pd-catalyzed cross-coupling of *p*-bromotoluene

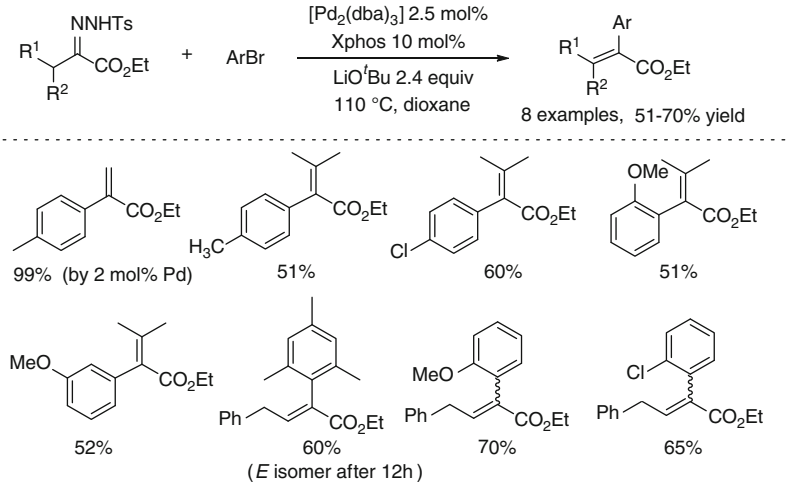


Fig. 10 Synthesis of substituted 2-arylacylates by cross-coupling of α-carbonyl tosylhydrazones with aryl halides

with tosylhydrazone of ethyl pyruvate was completed in quantitative yields utilizing catalytic $Pd_2(dba)_3$-Xphos (Fig. 10) [91]. It is notable that the potentially sensitive ester functionality remains intact under the basic reaction conditions. The scope of the reaction can be extended to several tosylhydrazones derived from α-alkyl 2-oxoesters. The reaction of linear 2-oxoesters leads to a mixture of *Z/E* isomers and the ratio is affected by the size of groups on the double bond. The bulky *E*-mesitylene in the mixture undergoes isomerization and finally affords exclusively *E* isomers if the reaction is carried out for longer time.

Attempts have also been made to develop a more practical procedure by carrying out the reaction directly from ethyl pyruvate through a one-pot process (Fig. 11). The crude tosylhydrazones, freshly formed by stirring the mixture of ethyl pyruvate and tosylhydrazide for 2 h at 70 °C, was employed for the coupling reaction in a one-pot protocol. A series of 2-arylacylates was synthesized through this reaction.

Thus α-functionalized alkenes can be conveniently prepared through the reaction of α-functionalized tosylhydrazones with aryl halides. More related reactions of corresponding α-substituted tosylhydrazones with aryl bromides have been reported by Barluenga and co-workers (Fig. 12) [92]. With $Pd_2(dba)_3$-Xphos, the reaction was carried out from tosylhydrazones (method A) or directly from ketones in one-pot fashion (method B). The coupling reaction of aryl bromides bearing a variety of substituents on the aromatic ring leads to expected enol ethers or enamines in good yields. Less reactive chloride on the aromatic ring of aryl bromide is tolerable in the reaction with exclusive chemoselectivity. In the reaction of 1,2-dibromobenzene, one of the bromo substituents undergoes coupling reaction and another remains intact to give *o*-bromo-substituted enol ether. It has been observed that ketone substrates lead to the mixture of *E/Z* isomers in approximately 1:1 ratio and the aldehyde substrates mainly give *trans* olefins. As previously

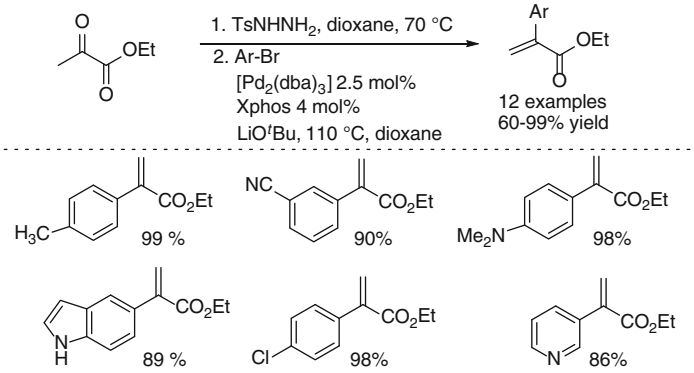


Fig. 11 Synthesis of 2-arylacylates by one-pot reaction of α-carbonyl esters with aryl halides

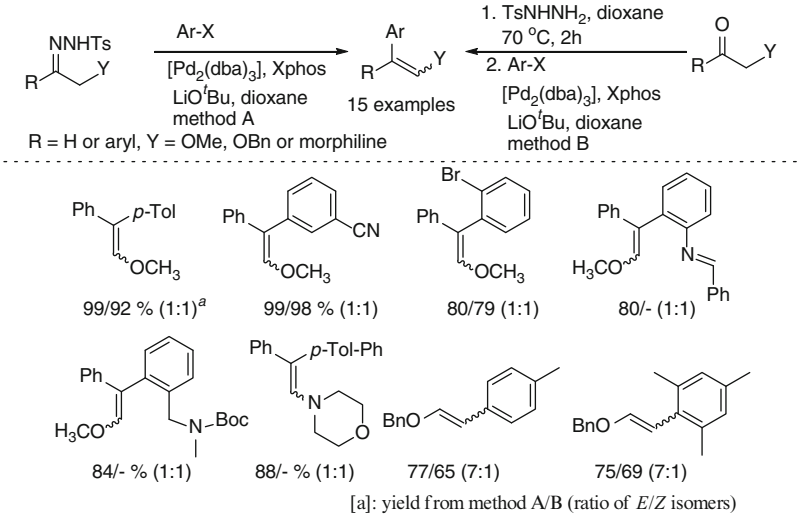


Fig. 12 Synthesis of enol ethers and enamines by reaction of α-substituted tosylhydrazones with aryl halides

discussed, the stereochemistry is determined in the step of β-hydride elimination. In this reaction, good stereoselectivity can be obtained when there is significant steric interaction between R and Ar groups – see (12). Enol ethers, which can also be obtained in this reaction, are commonly used intermediates in organic synthesis. These compounds can be further hydrolyzed to generate corresponding carbonyl compounds by treating with acid [92].

The reaction of tosylhydrazone derived from 1-methyl-2-hexanone ketone containing hydrogen atoms on both α-carbon atoms has also been mentioned in the same paper. A mixture of enol ether and allylic ether in 1:1 ratio without *Z*/*E* selectivity is produced because of the lack of regioselectivity in the step of *syn*

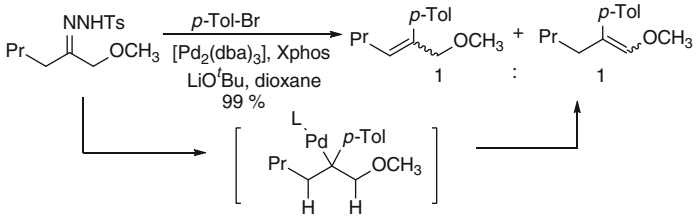
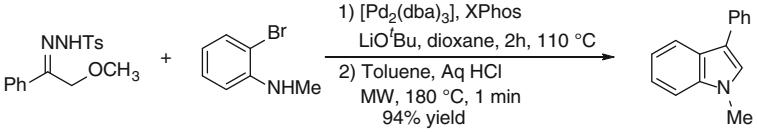


Fig. 13 Studies on regioselectivity of *syn* β-hydride elimination

β-hydrogen elimination (Fig. 13). The heteroatom on the α-carbon of hydrazone does not have any obvious influence on the regioselectivity.

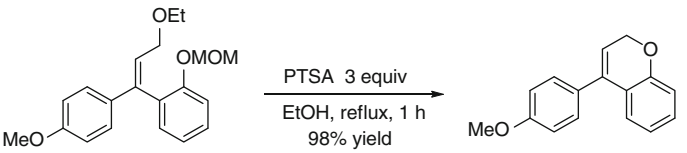
In addition, the coupling reaction of 2-methoxyacetophenone with *o*-bromo-*N*-methylaniline has been applied to prepare indole derivatives, by combining the coupling reaction with acid promoted C–N bond formation – see (14).



(14)

Alami and coworkers reported the Pd-catalyzed cross-coupling reaction of *ortho* substituted aryl halides with tosylhydrazones bearing ethoxy group on β- or remoter positions (Fig. 14) [93]. Tosylhydrazones were freshly prepared by a one-pot two-step process including alkynes hydration and tosylhydrazones formation. It is notable that high yield of *Z*-trisubstituted olefins can be isolated as main product. As already mentioned, the stereoselectivity is determined in the step of *syn* β-hydride elimination of the palladium intermediate. Experimental results suggest that an *ortho* substituted aryl group and adjacent substituent are required for a *cis* arrangement in the transition state for β-hydride (Fig. 14). The intriguing *ortho*-directing effect has been confirmed with DFT calculation by Barluenga and coworkers [75, 94]. The details will be discussed in Sect. 3.3.1.2.

The allylic ethers obtained can be further used to prepare 4-arylchromenes, thiochromenes, and other related heterocycles through acid promoted C–O bond formation – see (15).



(15)

Metal carbene transformations of α,β-unsaturated diazo compounds or their precursors are generally complicated because of the possible competing intramolecular cyclization of diazo substrates [95–97]. This side reaction can be partially restrained by protecting the terminal olefin or placing the α,β-unsaturated moiety in

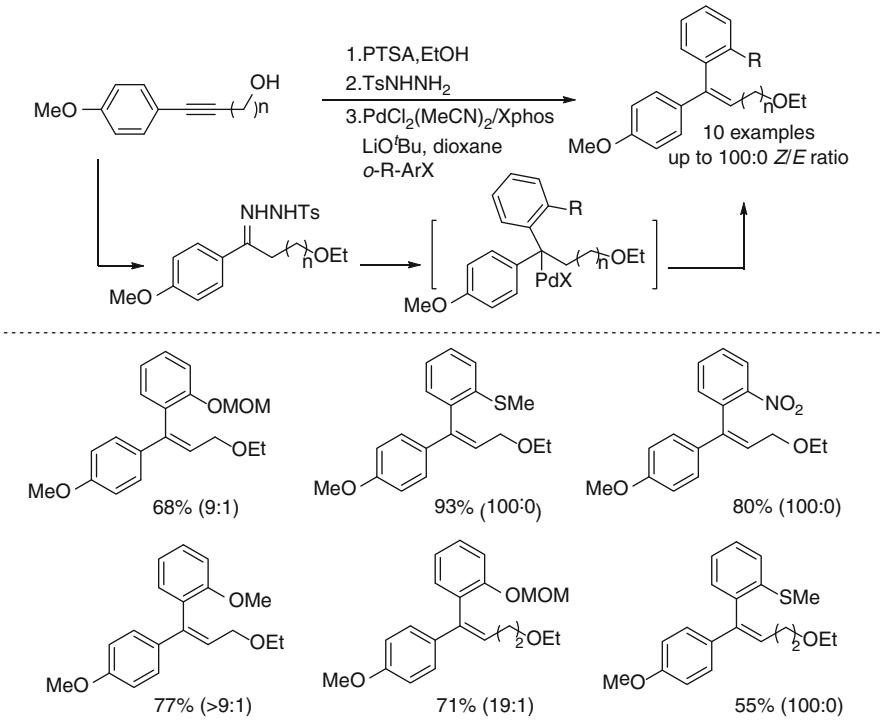


Fig. 14 Pd-catalyzed reaction of tosylhydrazones with *ortho* substituted aryl halides

a cycle. Barluenga and coworkers have recently reported the Pd-catalyzed cross-coupling of stable α,β-unsaturated tosylhydrazones with aryl halides, directly starting from α,β-unsaturated ketones (enones) (Fig. 15) [98]. The catalytic system condition $Pd_2(dba)_3$-Xphos-LiO^{t}Bu was applied to various substrates and conjugated dienes could be obtained in good yields. No products through competing intramolecular cyclization were detected in the reactions. The formation of dienes proceeds smoothly.

It is notable that two different types of dienes have been produced depending on the structure of α,β-unsaturated substrates. Similar reaction mechanisms can be proposed: oxidative addition-Pd carbene formation-migratory insertion affords intermediate **E**. Diene **A** is released with subsequent β-H elimination for the cyclic or linear substrates without hydrogen at the δ-position. Otherwise, complex **E** prefers to undergo η^1–η^3 rearrangement to give intermediate **G** for cyclic substrates. Diene **B** is then generated from **F**. Experimental results show that dienes **B** will be produced dominantly when enone moiety locates in a ring (Fig. 16).

Minor **A**-type diene would be generated if the original C=C bond located outside the ring of the cyclic ketone – see (16). Therefore the regioselectivity of this reaction is also influenced by the relative position of C=C and C=O bonds. In this case, the chiral center in the β-position remains intact.

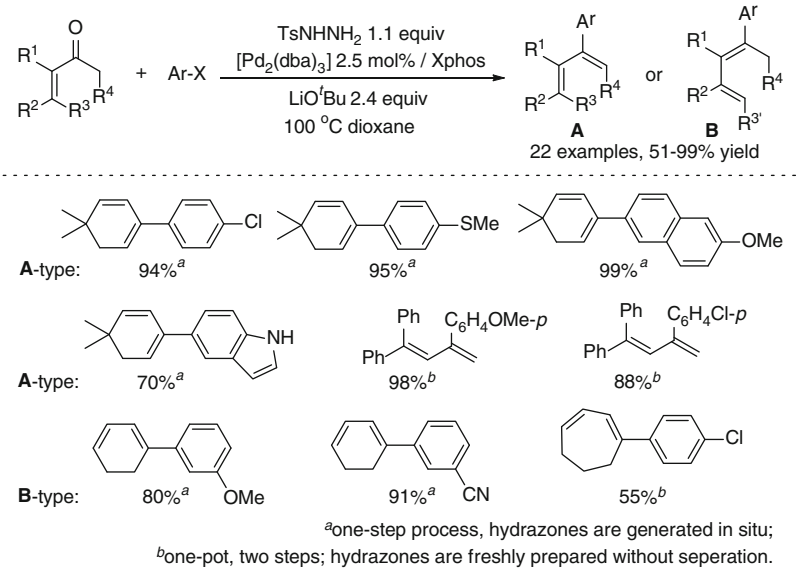


Fig. 15 Synthesis of dienes by reaction of enones with aryl halides

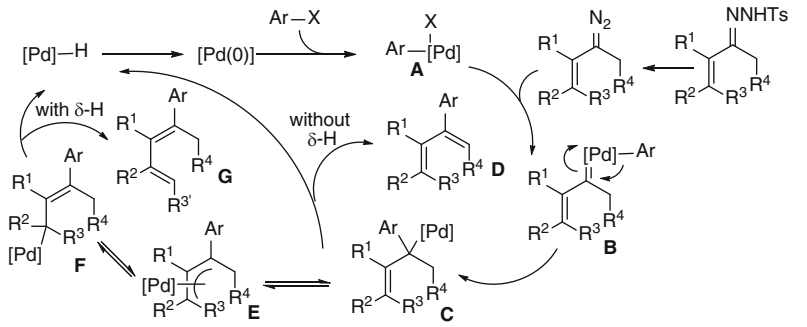
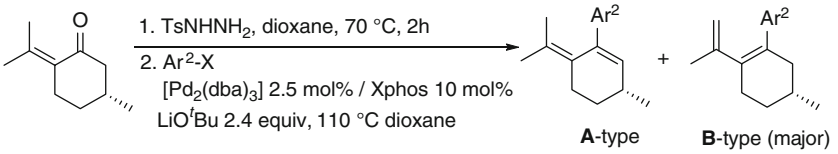


Fig. 16 Proposed reaction mechanism



(16)

The handling of chirality is an important topic in current synthetic chemistry. In this context, the synthesis of alkenes containing chiral moiety has attracted great interest. No chirality is introduced in the formation of C=C bonds through Pd-catalyzed cross-coupling. However, the existent chirality of substrates may be retained if the proton in chiral carbon is not involved in the step of β-hydride

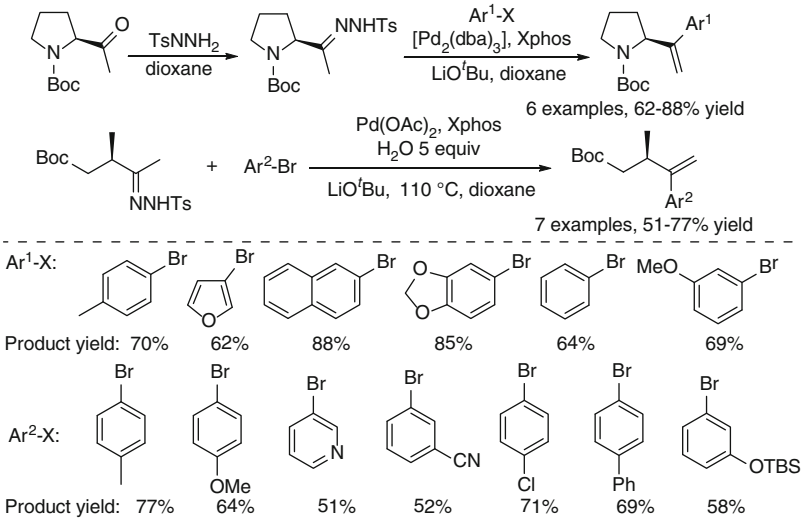


Fig. 17 Synthesis of α-chiral alkenes by reaction of α-chiral ketones with aryl halides

elimination. In 2010, Barluenga and co-workers reported the Pd-catalyzed coupling reaction of α-chiral methyl ketones with aryl halides through a one-pot procedure. Efficiently catalyzed by the $Pd_2(dba)_3$-Xphos combination, α-chiral alkenes have been prepared with complete retention of configuration of chirality at the α-position (Fig. 17) [99].

It is obvious that the chirality will be eroded if the β-hydride elimination occurs at the chiral α-position of tosylhydrazones. The selectivity of β-hydride elimination in this reaction can be interpreted as follows. Alkylpalladium complex, the intermediate generated after migratory insertion of palladium carbene, is favorable to afford 1,1-disubstituted chiral olefin (Fig. 18, path *a*) because of the less steric interactions in the transition state at β-hydride elimination. Apparently the alternative *syn* β-hydride elimination will lead to the erosion of chiral center. However, the latter pathway is not preferred because it leads to the eclipse of the bulky substituent with the methyl group of the substrate (Fig. 17, path *b*).

Nevertheless, the regioselectivity will be a problem for the substrates containing hydrogen on two unsymmetric α-carbon atoms (Figs. 4, 13, 15, and 19) [87, 92, 99]. Comparing the results of limited cases, it seems to indicate a tendency of preferential β-H elimination in secondary C–H over primary C–H and primary C–H over tertiary C–H (Figs. 16, 17, and 18). This tendency partially illustrates the retention of configuration in Fig. 17 [99]. Therefore the stereoselectivity of the olefins is determined by both thermodynamic stability of the olefin product and configuration of palladium intermediate in transition state.

For the reaction of *N*-tosylhydrazones derived from chiral cyclic ketones, the regioselectivity is also well controlled by the substrate structures. Barluenga and coworkers reported the synthesis of several enantiomerically enriched allylic ethers without chirality erosion through the coupling of aryl halides with α-chiral cyclic *N*-tosylhydrazones under the similar reaction conditions (Fig. 20) [99].

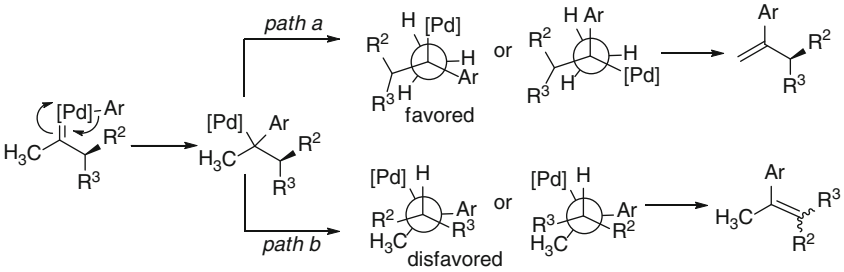


Fig. 18 Rationalization at the regioselectivity of the reaction

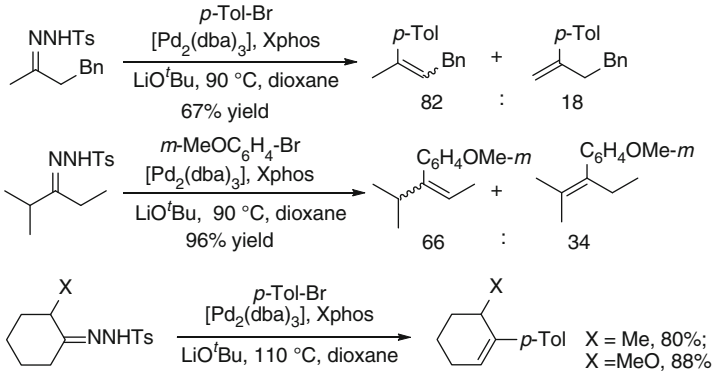


Fig. 19 Regioselectivity in the Pd-catalyzed reaction of tosylhydrazones with aryl halides

Moreover, a series of enantiomerically pure cyclic dienes has been synthesized through Pd-catalyzed coupling of aryl halides with β-chiral *N*-tosylhydrazones (Fig. 21) [98]. The reaction is carried out under the catalytic system $Pd_2(dba)_3$-Xphos with complete retention of the chirality. The mechanism of the diene construction has been illustrated in Fig. 16. Thus, it is predictable that only one type of diene can be produced starting from the cyclic enone (Fig. 21a). On the other hand, enones processing double bonds outside of the ring lead to two types of dienes (Fig. 21b) – see (16).

Cross-Coupling with Aryl Sulfonates

Aryl triflates have proved to possess approximately the same reactivity as aryl halides in various Pd-catalyzed cross-coupling reactions [100, 101]. In 2009, Alami's group employed aryl triflates for Pd-catalyzed coupling reaction of polyoxygenated aryl *N*-tosylhydrazones (Fig. 22) [102]. The catalytic system $Pd(OAc)_2$/Xphos with LiO^{t}Bu as base in dioxane was found to be suitable for the reaction. The reaction is initiated by the oxidative addition of aryl triflate to Pd(0) species. Then similar migratory insertion and β-hydride elimination subsequently take place to afford a series of 1,1-diarylethylenes which are of biological interest.

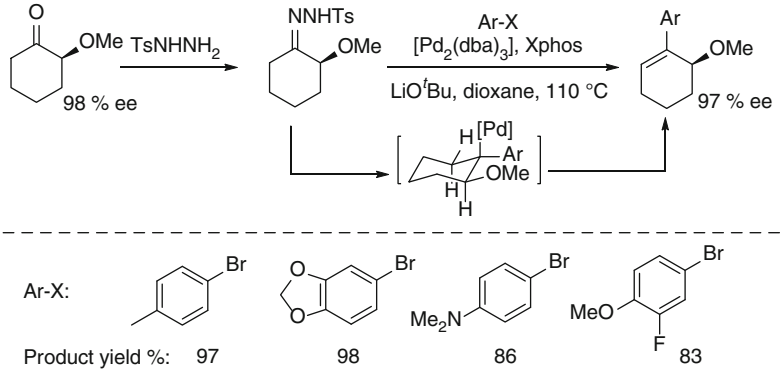


Fig. 20 Synthesis of chiral allyl ethers by reaction of α-chiral cyclic tosylhydrazones with aryl halides

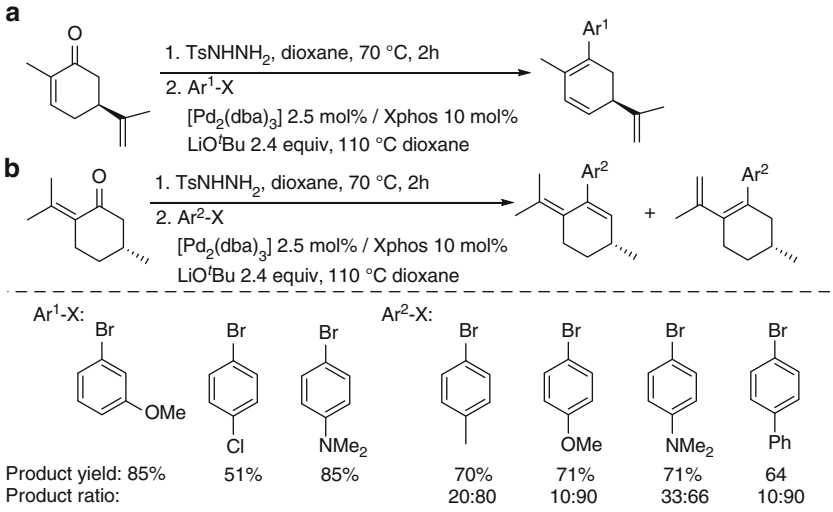


Fig. 21 Synthesis of chiral dienes by reaction of chiral *N*-tosylhydrazones with aryl halides. (**a**) reaction with cyclic enone; (**b**) reaction with enone

Moreover, the tendency of aryl triflate to be more reactive than nonaflate and imidazolylsulfonate in the reaction has been illustrated. Aryl tosylate has been observed to be inactive under this reaction condition.

In 2010 the same group reported another similar coupling reaction of tosylhydrazone with aryl triflate or aryl imidazolylsulfonate, catalyzed by $PdCl_2(MeCN)_2$-dppp-Cs_2CO_3 – see (13) [90].

Very recently, Barluenga and coworkers have reported that aryl nonaflates can be employed in the coupling with tosylhydrazones under the catalytic system $Pd_2(dba)_3$-Xphos-LiO^tBu, with an additional 5 equiv. of H_2O in dioxane (Fig. 23) [94]. Halide salt has been commonly utilized to accelerate the Pd-catalyzed coupling reaction of aryl sulfonates [100, 101]. This is also the case for the coupling reaction

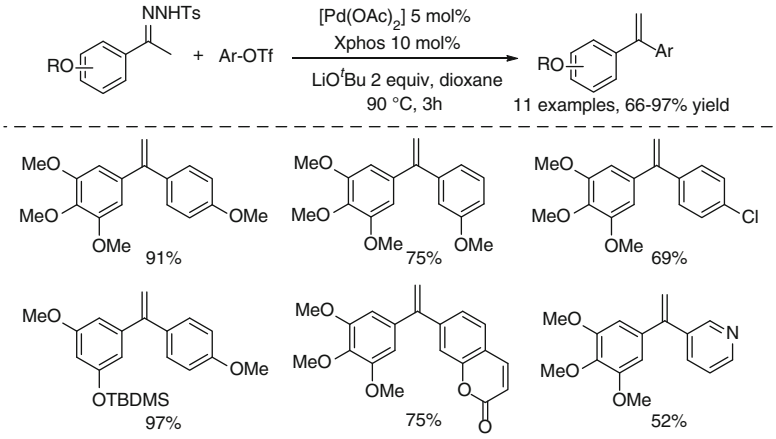


Fig. 22 Synthesis of 1,1-diarylethylene by reaction of tosylhydrazones with aryl triflates

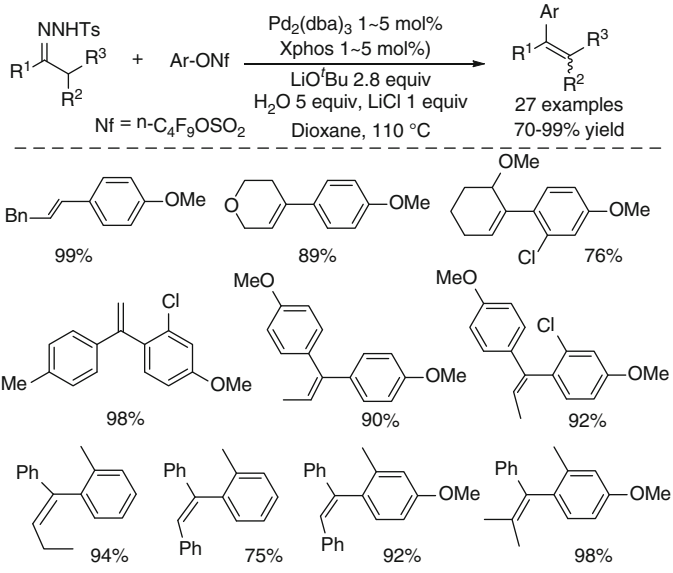
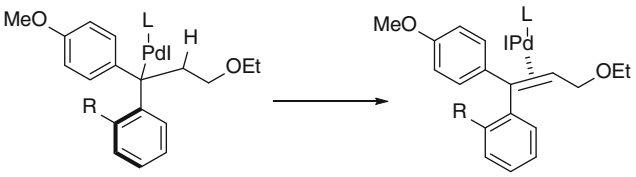


Fig. 23 Alkene synthesis by reaction of tosylhydrazones with aryl nonaflates

with tosylhydrazone. The experimental results indicate that 1 equiv. of LiCl is necessary to increase the reaction efficiency of alkyl tosylhydrazones. Moreover, 2 equiv. of tosylhydrazones have been used to avoid the Heck reaction of newly produced olefins. However, for the reaction of aryl tosylhydrazones with nonaflates, the coupling proceeds smoothly without LiCl.

The stereochemistry observed in this reaction provides useful insights into the reaction mechanism. *trans*-Disubstituted ethylenes have been isolated from the reaction of aldehyde tosylhydrazones with aryl nonaflates. The reaction of aryl nonaflates with tosylhydrazones derived from dialkyl ketones mainly leads to

E-alkene. These results are not consistent with the commonly proposed mechanism – see (12). However, the stereochemistry of the reaction with tosylhydrazones derived from alkyl aryl ketones is different. The reaction with *ortho*-substituted aryl nonaflates exclusively leads to trisubstituted *Z*-olefins. The results appear abnormal because that will need a *cis* arrangement between the *ortho*-substituted aryl and adjacent alkyl groups. Thus, the steric hindrance between *ortho*-substituted aryl and adjacent alkyl groups seems to be disadvantageous in the transition state for β-hydride elimination (Fig. 14). The authors have noticed this phenomenon and have carried out a DFT computational study to gain detailed insight into the reaction mechanism. The calculation on transition state indicates that the *ortho*-substituted aryl is almost orthogonal with the plane defined by the incipient double bond, placing the *ortho*-substituent *anti* with the palladium complex – see (17) [75, 93, 94]. This kind of outcome is termed an *ortho*-directing effect. Thus it is reasonable that similar reaction of aryl nonaflates possessing a *meta* or *para*-substituent leads to the mixture of *Z*/*E* 1:1 isomers without the *ortho*-directing effect.



(17)

Cross-Coupling with Aryl Boronic Acids

Wang and coworkers have reported the Pd-catalyzed coupling reaction of arylboronic acids with diazo compounds [84]. In 2010, oxidative Pd-catalyzed coupling of *N*-tosylhydrazones with arylboronic acids was reported by the same group (Fig. 24) [103]. Under the optimized conditions the reaction of a series of arylboronic acids with substituted acetophenone *N*-tosylhydrazones proceeds well to afford substituted olefins in acceptable yields. Experimental results indicate that no significant electronic effect and *Z*/*E* selectivity have been observed in the reaction.

In this reaction a combination of CuCl and O_2 is used as oxidant. The reaction is initiated by the oxidation of CuCl to Cu(II) species by oxygen, which then oxidizes Pd(0) to Pd(II) species (Fig. 25). Subsequently, similar Pd carbene formation and β-hydride elimination take place to afford the olefin products.

3.3.2 Carbene Insertion into the Palladium–Vinyl Bond

Pd-catalyzed coupling reaction of vinyl halides with diazo compounds has been proven to be an efficient process to synthesize substituted olefins with good stereoselectivity [78–80]. In 2010, Barluenga's group reported the Pd-catalyzed coupling reaction of vinyl halides with *N*-tosylhydrazones for the preparation of dienes in moderate yields (Fig. 26) [98]. The reaction follows a similar mechanism: oxidative addition and the

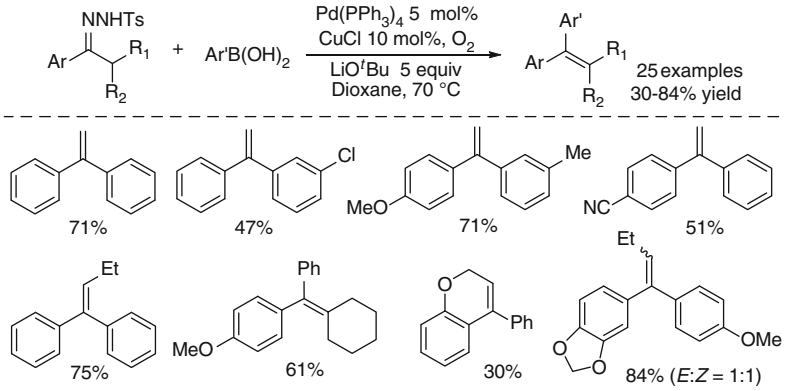


Fig. 24 Oxidative cross-coupling of *N*-tosylhydrazones with aryl boronic acids

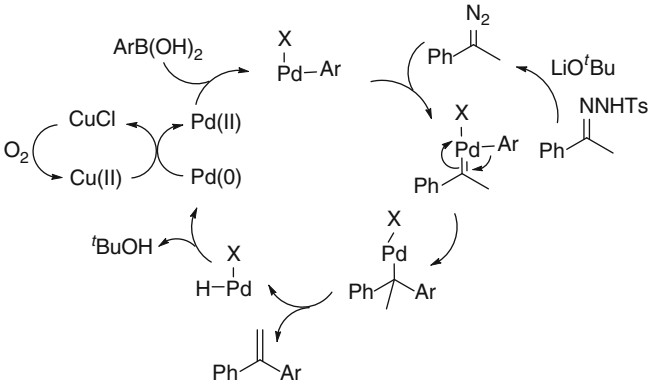


Fig. 25 Proposed reaction mechanism

migratory insertion take place to generate the palladium intermediate. Subsequently, a η^1–η^3 rearrangement occurs. Then β-hydride elimination takes place which finally leads to conjugated diene. The important feature of this type of coupling reaction is that π-allylic Pd complex is generated through Pd carbene migratory insertion.

3.3.3 Carbene Insertion into the Palladium–Alkynyl Bond

In 2011, Wang and coworkers reported the oxidative Pd-catalyzed reaction of tosylhydrazones with terminal alkynes (Fig. 27) [104]. Catalytic system $Pd(OAc)_2$-P(2-furyl)$_3$ was successfully utilized for the reaction in the presence of LiO^tBu and benzoquinone (BQ).

The reaction is initiated by the insertion of Pd(II) complex into the C–H bond of the terminal alkyne to give palladium alkynyl intermediate. Then complexation with in situ generated diazo compound occurs to form a palladium carbene intermediate. Subsequently, Pd carbene migratory insertion into the Pd–alkynyl bond

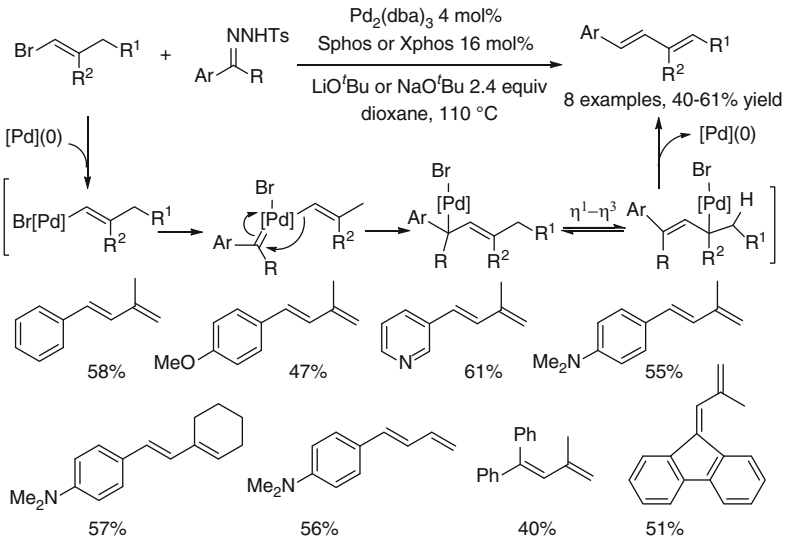


Fig. 26 Synthesis of liner dienes by reaction of tosylhydrazones with vinyl bromides

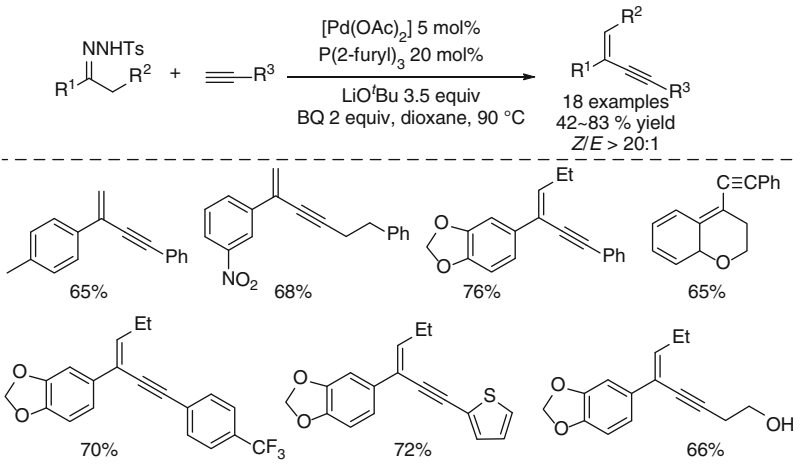


Fig. 27 Synthesis of conjugated enynes by oxidative coupling of tosylhydrazones with terminal alkynes

occurs, followed by β-hydride elimination to afford conjugated enynes in good yield with regeneration of Pd(0). BQ is employed to oxidize the regenerated Pd(0) into Pd(II) for another cycle (Fig. 28). The configuration of conjugated enynes has been determined by ^{1}H NMR and the ratio of *Z*/*E* has been found to be up to 20:1 in most cases. The *Z*-enynes stereoselectivity is also determined in the step of *syn* β-hydride elimination. The linear alkyne is favored to eclipse with the R^2 group that avoids the steric interactions between R^1 and R^2 (Fig. 28).

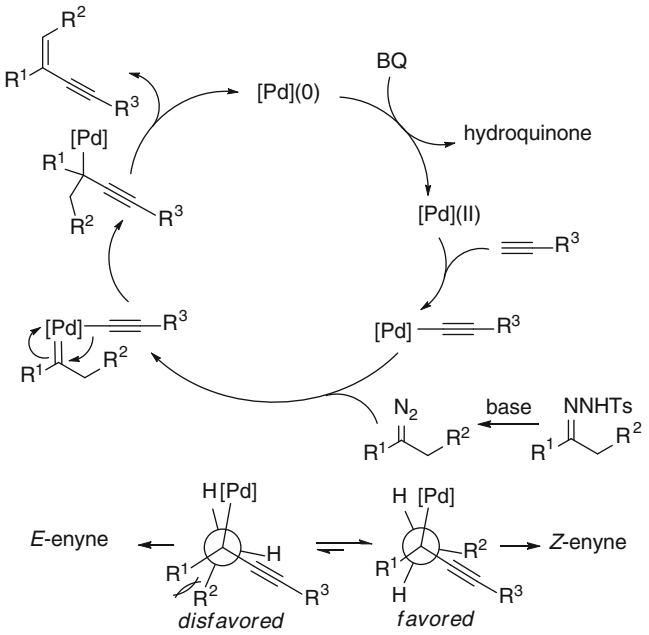


Fig. 28 Mechanistic rationale

3.3.4 Carbene Insertion into the Palladium–Allenyl Bond

Liang and coworkers recently reported the Pd-catalyzed cross coupling between propargylic carbonates and aryl ketone tosylhydrazone salts (Fig. 29) [105]. The reaction with secondary or tertiary carbonates was catalyzed by $Pd_2(dba)_3$ in the presence of PTC and led to corresponding vinylallenes. However, the scope of reaction could not be extended to primary carbonates. Moreover, trace product was isolated from the reaction of propargylic carbonates possessing an electron-withdrawing group on the aromatic ring. Moderate to good yields were achieved for the substrates containing electron-donating group on the aromatic ring.

Weak base such as cesium carbonate has been utilized in this reaction to generate diazo compounds in situ from tosylhydrazones through the Bamford–Stevens reaction. The reaction is initiated by palladium-promoted decarboxylation of propargylic carbonate to form propargylpalladium complex **A**, which then tautomerizes to afford allenylpalladium intermediate **B**. Subsequently, the common carbene formation-migratory insertion-β-hydride elimination occurs to afford various vinylallenes (Fig. 30).

However, by-products were also observed in this reaction, which was due to the direct reaction of tosylhydrazone with palladium intermediate **A**. The reaction of propargylic carbonates and aryl ketone tosylhydrazones leads to substituted propargylic *N*-sulfonylhydrazones when catalyzed by the different catalyst combination $PdCl_2(CH_3CN)_2$-dppp in the presence of Cs_2CO_3. This side reaction might be caused by the use of weak base Cs_2CO_3. Under such conditions, Pd-catalyzed amination of

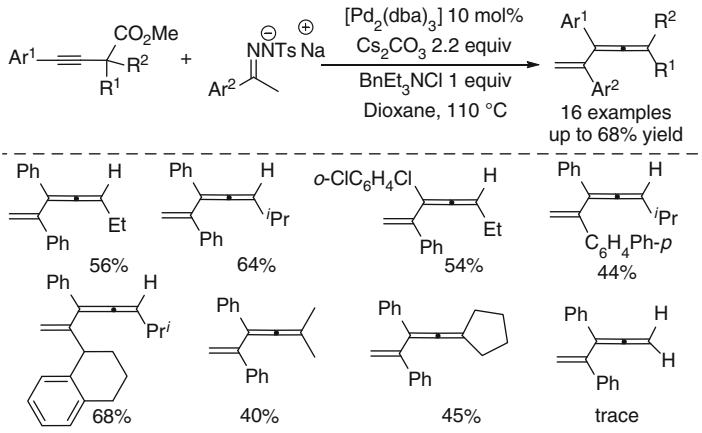


Fig. 29 Synthesis of vinylallenes by reaction of tosylhydrazones salts with propargylic carbonates

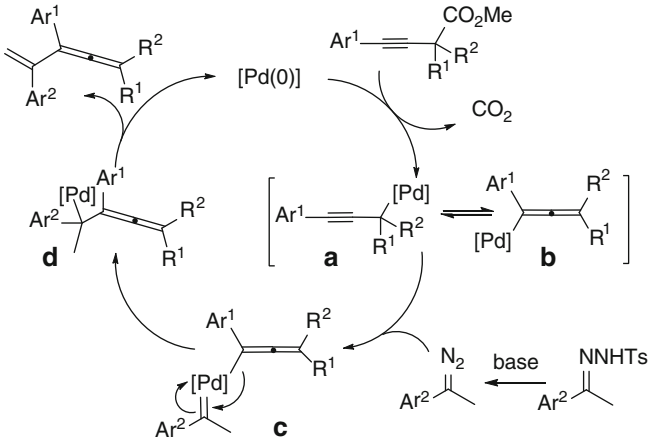
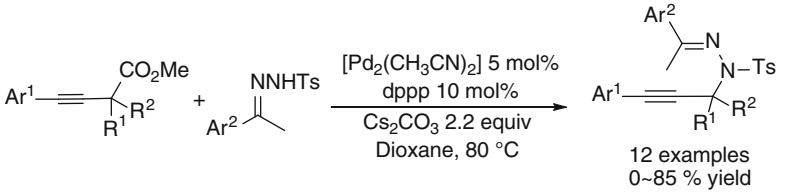


Fig. 30 Proposed reaction mechanism for vinylallene formation

tosylhydrazones becomes more competitive than Pd carbene formation because of the low concentration of the in situ generated diazo compounds – see (18) [4, 5].



(18)

3.3.5 Carbene Insertion into the Palladium–Benzyl Bond

The coupling reaction of α-diazocarbonyl compounds and benzyl bromide developed by Van Vranken's group provides a convenient method for the synthesis of substituted olefins [73, 82]. The corresponding coupling reaction of *N*-tosylhydrazones with

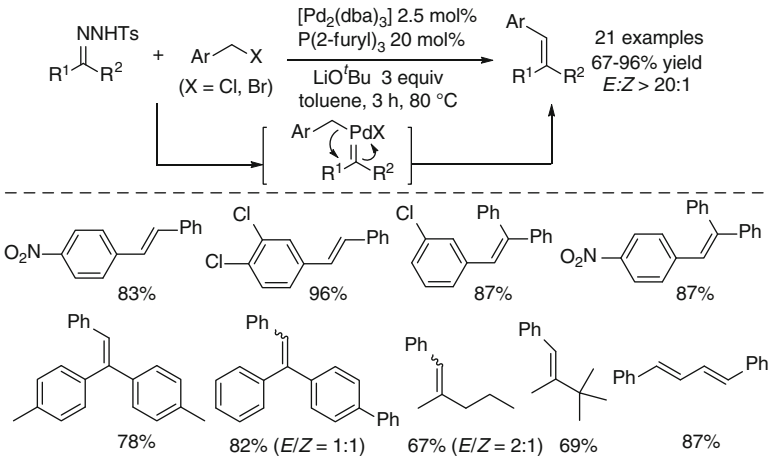


Fig. 31 Synthesis of olefins by reaction of *N*-tosylhydrazones with benzyl halides

benzyl halides has also been developed. A series of substituted olefins has been obtained with excellent stereoselectivities and yields by using the $Pd(OAc)_2$-P(2-furyl)$_3$ system as the catalyst (Fig. 31) [106]. It is notable that the reaction goes through smoothly no matter whether the *N*-tosylhydrazones are derived from alkyl aldehydes, aryl aldehydes or ketones. A chloro-substituent on the aromatic ring of either *N*-tosylhydrazones or benzyl halides is compatible under the reaction conditions. A similar mechanism is also proposed. The reaction is initiated by oxidative addition of palladium(0) complex to benzyl bromide. β-Hydride elimination is then followed by the migratory insertion of palladium carbene into the palladium–benzyl bond. The stereochemistry of the products is also determined in the β-hydride elimination step. *trans*-Olefins can be obtained by the reaction of tosylhydrazones deriving from aldehydes. In addition, *trans*, *trans*-dienes can be synthesized by the reaction of α,β-unsaturated aldehyde tosylhydrazones. Moreover, *E*-selective olefines are exclusively formed when the sizes of the two groups on the carbon of ketone hydrazone are distinguishable. Otherwise, the *E*, *Z*-selectivity will be diminished.

3.3.6 Carbene Insertion into the Palladium–Acyl Bond

In 2010 Wang's group reported a three component reaction of ketone tosylhydrazones, aryl iodides, and carbon monoxide [107]. At the beginning of the investigation the mixture of enones and carbonyl compounds was formed. Further examination found that the chemoselectivity of the reaction could be controlled by the catalyst (Fig. 32). Catalyst system $Pd_2(dba)_3$-$[HPCy_3]BF_4$ led to the enone derivatives exclusively. In contrast, carbonyl compounds were obtained in the presence of $Pd(PPh_3)_4$ and Et_3SiH. Under either of the two sets of reaction conditions, high chemoselectivity was achieved.

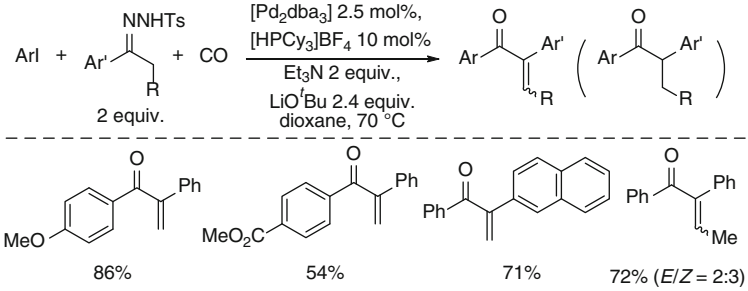


Fig. 32 Synthesis of enones by reaction of three-component reaction of ketone tosylhydrazones, aryl iodides and CO

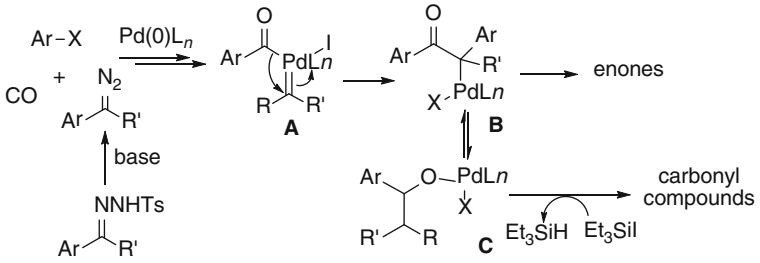


Fig. 33 Proposed reaction mechanism

A possible mechanism involving common oxidative addition, CO insertion, and decomposition of diazo compounds was proposed. The generated complex **A** undergoes a carbene migratory insertion into the palladium–acyl bond to form C-bound enolate **B**. Subsequently, β-hydride elimination of complex **B** releases enone. For the equilibration between intermediate **B** with *O*-bond enolate **C**, the latter is favored with the aid of strong electron-donating ligand PCy_3. Therefore, the transmetallation with Et_3SiH and reductive elimination consequently take place to afford carbonyl compounds (Fig. 33).

4 Closing Remarks

As discussed in this chapter, various methodologies for C=C bond formation have been developed based on the reaction of *N*-tosylhydrazones. Traditional base promoted reactions such as the Bamford–Stevens reaction, the Shapiro reaction, the Barton–Kellogg reaction, and Julia-type condensation–fragmentation have already been widely applied for organic synthesis in the past few decades. The palladium catalyzed reaction of *N*-tosylhydrazones through metal carbene intermediates has attracted increasing attention in recent years. *N*-Tosylhydrazones are readily available substrates and are stable. They have been proven to be reliable

reagents as diazo precursors. Since palladium is the most versatile metal in cross-coupling reactions, various approaches for the generation of palladium species have been developed. It is thus expected that more reactions of Pd-catalyzed cross-coupling of tosylhydrazones will emerge [108, 109]. With rapid development of palladium catalyzed cross-coupling of *N*-tosylhydrazones with various substrates, this type of reaction has the potential to become practically useful methodology for the formation of functionalized C=C bonds.

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